						H95242, AA172161, AI888638, AI817694, AI366890, AI026962, AW148873, AW372205, AW439756, AI799210, AI339271, AI367802, AI565761, AI422942, AI815783, AW029098, AW130765, AI640433, AI392827, W67741, AI421728, AA564386, W77958, T49431, AA886636, H19721, AA931069, AI587063, AI538865, AA911757, AA844319, H10384, AI024999, AI205206, AA907497, AW191862, W45437, AA854454, AA827211, AI357050, W58732, AA864255, F24893, F36657, AA600782, AA319276, AI302198, AA134930, T40697, AA939271, AI339101, AI268568, AI268513, AA676629, AI424652, T23067, W72214, W67761, T15455, AW078588, AI015096, AA652639, AW009699, R41394, AA858041, T91991, T39608, AI865868, AA236441, R69121, AW075784, N85194, AA682375, W17051, AI568256, AA555128, AW191881, AA130364, AA600778, AA725773, AA808374, AI691156, AA552013, AA780860, T39610, AA586795, AI833065, AI701299, AW383883, W52014, AA863193, AA984388, W74143, AI343015, AW295572, AL039378, F32010, AA827536, AA832110, AI827029, AA737632, AA748445, AI283017, AA723536, R41283, H60450, AA052977, AI358413, AI334792, AA009996, AI452850, AI375377, AI248684, AI092250, AA642323, AA847164, AI359493, AI990198, AW088914, AA349440, AI674436, W85690, W80752, AI567578, AW003662, AA515597, AW024419, AA789190, AI955939, AA548671, AI347012, AI357262, AI659567, AA769657, AI689260, AA872184, AI824151, AA701479, AI973118, AA279182, AA838044, AA614311, AI955325, AA076347, AI625537, H17419, AW245328, AI801747, AI955399, AW072450, AI571032, AA642219, R17919, AI832421, AA069177, F13645, AW245586, AA548861, AW083759, F34935, AL137377, AC004472, M30143, AF122048, and AF100752.
HCFNQ62	9306	745755	1 - 470	15 - 484		W84708, AI936823, AW137975, N68257, AA443187, AI417796, AA657780, H89014, H88792, AA586672, AL044918, and AL117474.
HCFNP09	9307	961149	1 - 659	15 - 673		AI824052, AA036889, W81555, AI694971, AI863745, AI864321, and AA036888.
HCFNJ34	9308	485822	1 - 503	15 - 517		AW007318, AI949612, AI497946, AI628977, AL119391, AW392670, AL119443, AL119497, U46351, U46349, U46347, AL119324, AL119319, AL119522, AW363220, AW384394, AL119483, AL119457, U46350, AL134527, AL119484, AW372827, AL119444, Z99396, AL119439, AL119363, AL119355, AL119418, AL119401, U46346, U46341, AL119341, AL119335, Z84480, AC004609, AC006313, AR060234, AB026436, AR066494, A81671, and AR054110.
HCFNG63	9309	745148	1 - 232	15 - 246		AA515905, AA507824, AI355206, AW023990, AA603445, AA580808, AI732120, AI284640, AA226305, AW276435, AW021583, AA658362, AW238278, F34498, AI860020, AA856954, AA613227, AI537955, AA680243, F01314, AW089322, AA908468, AA502155, AI133164, F17891, AA551553, AI564454, AA847622, AI863054, AI243584, AA092602, AI358571, X75335, D83989, X55923, U67829, U67827, M87922, M87891, U67828, AF077058, S42655, AC005523, AC005050, Z31000, AL023575, AL024507, AP000023, AC004257, AL133353, AC003663, M87919, AL035398, AC005288, AC008033, AL008718, Z98946, AL022324, AL031321, AC007406, AF010317, AC007731, AP000039, AP000107, AC005500, AL049692, AC006275,

					AC006480, AC005944, Z69707, AC005387, AC005081, AC007226, AL096791, AL050341, AF196779, AC004408, AF134726, AL020993, AL008726, AL078475, AC003030, AC005102, AC005730, AL031295, AC007676, AC008079, AB026584, AC007227, AC018633, AC004638, AC005832, U49740, Z98752, AF106202, AP000298, U96629, AC005529, AC005300, AC006004, AL022170, AL080317, AP000025, Z93241, AC008372, AL049776, AC004531, AP001114, AC009516, Z84572, AP001065, AC000085, AP000694, U69570, AC007191, U91326, L26261, AC007386, AC006271, AL008719, AL022237, AC004837, AL008635, AC004230, AC003043, Z83822, AF039907, AL021878, AC005231, AF038458, AC005745, AL096703, AF109907, AF141309, AC002350, AC005218, L34079, AP000280, AC000353, AC004492, AL080242, AC004019, X71875, AF001549, AC005332, AC004856, AC006312, AC004652, AF015156, AC004821, AC003684, AC004675, AC002126, AC006512, AL132777, AC004039, AC005331, AC005703, AL109914, AL031280, AC002558, AP000557, AC005004, AC005754, AC006511, AL121754, AC004034, AL031577, AL096774, AL022163, AL008715, AL009181, AL096843, AC007919, AB003151, AC005625, AC004475, AC006536, AC004703, AC005399, AL031282, and AC012085.
HCFNG10	9310	848225	1 - 1653	15 - 1667	AA452506, W94343, AA488471, AA761766, AI271809, AI673242, AW295352, AA211131, AW084027, AA211130, W94373, AI972578, AI675734, AA211710, AI657152, H93180, AA442937, AW197446, AA436769, AA385636, AA033875, AA421160, AI650629, AA417770, AA306761, AI054242, AI261197, AA829487, AA417236, AI335132, AI053468, R29693, W94372, AW020931, AA715307, AA809974, AI540890, AL121270, AW020592, AL121328, AW019988, AI923509, AW023863, AW021178, AW020425, AI879064, AI624543, AW189802, AI557238, AI525653, AW020406, AW021777, AW021693, AW019985, AW020328, AW022826, AW022299, AI064830, AW023351, S68736, and A91160.
HCFNB09	9311	625697	1 - 191	15 - 205	H49917, and AC007537.
HCFNA77	9312	874777	1 - 265	15 - 279	AL041196, AI347284, AA861637, W02835, AA863177, AI818167, AI248206, AA987274, AA338877, AI199674, N29825, AW131788, AI953166, AI567464, AI025214, AI885412, AA568780, AI174734, AW138007, AW007757, AA193266, AW027175, AA614090, AL046529, AW058096, AI278213, AW169713, AI571295, AW083404, AI873719, AA864580, AI471327, AA603136, AI383280, N70535, AA255990, AI091040, AI763223, AA761693, AA309912, AA826815, W05581, AA229402, AA229290, AI631521, AA861300, AI969567, AI373276, AW059713, AA256252, AW020876, AI376180, AI468873, AW029401, AW081231, AI923768, AI619817, AI373622, AI828734, AW008737, AI627893, AW243619, AI354627, AI610115, AI918376, AI874243, AW084117, AI932818, AI633308, AI742068, AI738660, AI540474, AI679211, AA848053, AI922278, AI334820, AI570989, AI619485, AI583308, AW055081, AI247298, AI933783, AA766618, AI583065, AI828806, AL122045, AF047443, AL122049, A57389, U94316, AL080156, E05822, S61953, A27171, AL133049, U49434, AF118070, AL137539, AL133624, AC007458, AL137300, AF182215, AJ131955, X95876, A65965, D00174,

					A65943, U75378, AF113676, AL049465, AL122098, Y08616, S68736, AF085809, AF108357, X72387, AC004987, AC005156, AF012536, E15582, AF084644, AF084645, AF106934, AC005876, AL080074, AL117432, AL137556, I33391, and AF017152.
HCFNA64	9313	850391	1 - 523	15 - 537	AA424916, and AI783939.
HCFNA21	9314	671021	1 - 244	15 - 258	AA640305, AA595661, AA493464, AW275432, AI224583, AA601376, AW021674, AA425283, AI051670, AA669238, AI086603, AA102054, AA084439, AI690379, AA604601, AI355246, R43468, AI754064, AI926102, AI732501, AI791457, AA526415, AA180056, AW104161, AW151541, AA747234, AI791659, AI521525, AI702049, AA313025, AW023390, AW265468, AA847504, AI433952, AA199578, AW151247, AI590442, AA573067, AA555232, AI755227, AI524453, H82636, AA559219, AW020150, R42954, AA525753, AI090377, AI865087, AA019973, AI267416, AA602105, AI801563, AI568376, AA603359, AI174703, AA649641, AI753904, AI056566, AA491827, AI267269, AA831426, AA489390, AL048969, AI065031, AA054085, AA582073, AA101265, AA018207, AA013168, AW192419, AW148821, R22196, AW264245, AI926104, AA084609, AA598443, AA664963, N95424, AW277093, N23893, AA493808, AW327801, AA642809, AI344906, AA746951, AL042282, AW410561, AA298365, AI572680, AI431442, AA083003, N29105, AA570255, AA586474, AW057760, AA515048, R62701, W04238, AI887468, AA703818, AA601712, AA767942, AA584765, AL041375, AW028089, AW072963, AI251024, AI753131, AA832357, AA515165, AL121039, AW084173, AI859368, AA228274, AW238341, AA666295, AI291437, AA661583, AA689351, AL037067, AI803809, AA502022, AA533066, C14614, AA502532, AL119010, AA128511, AI760835, AI299445, AA810158, AA507623, AI732120, Z84466, AC005800, AC007216, U95742, AC005940, U91318, AC002312, AC006236, AL031284, AC004125, AC003041, AC004910, AL096763, AL080243, Z97184, AC005971, AC003042, AC005225, AC004895, AC005189, AC004821, AC007546, AC002301, Z86090, Z83826, AC003108, AC004973, AP000359, AB023050, AL020993, Z95114, Z93244, AC006121, AC002347, AF111168, AF047825, AC007050, AL031594, AC002544, AP000511, AC006241, AC003010, Z93017, AC005104, AF030453, AC003030, Z96074, Z98044, AC005553, AF196969, AC007052, AC005484, AC007437, AC005231, AP000555, AC003043, AC004962, AF217403, Z98200, U85195, AC016831, AC005911, AL022476, AC002476, AL049776, AC007225, AE000658, AL109963, AC007308, AC016027, L44140, AC005632, AC005082, AC003101, AL049757, X55448, AC006449, AC006538, Z84480, AC006441, U52112, AL109827, AC005696, AC005736, AC005703, AC007041, AC008132, AC004797, AC005037, AL031662, AC006251, AC004598, AC002091, AL035398, AL022334, AC006132, U95739, AC004000, Z82215, AC004663, AC002429, AL031123, AC007676, AL121754, AL021392, U82668, AC016830, AC002314, AC004605, AL135744, AL079295, AF001549, AC006312, AC005102, X62355, AD000812, AC005207, AC009247, AC004911, AL121825, AF196779, AL008637, AC006115, AC004217, AC003007, AC002996, AL035425, AL009051, AC005520, AL031427, AP000558, AC006167,

						AL021154, Z83851, AC005088, AL009181, AC005255, Z93024, AC007993, AC004883, AC004699, AC006252, AC005874, AF134471, Z83838, AC005369, AC005841, AC005237, AL008582, AC005599, AL035079, AL049539, AP000085, AC006070, AC005015, Z99716, AL022323, AC007298, AC005803, AC004874, AL024498, AP000510, AD000092, AC005730, AL049694, AP000350, AC006006, AF053356, AC008372, Z97056, AC003029, AC004019, AC007686, AF134726, AC004069, AC006536, AC005914, AC005247, AL022322, AC004817, AC005049, AC008126, AC002126, AL031767, AC006211, AC005003, AL031680, AL078471, Z98742, AL049794, AC004854, AC005005, AC005899, AL031584, AC003006, AC006315, AL049745, AL109627, AC002302, AP001054, AC005837, AL109984, AP000512, AC012085, AC004961, AL136295, AP000127, AP000205, AC005529, AL096791, AL031447, AL133244, AF042089, AC007395, AL078584, AC006511, AC020663, AC004383, AL050332, AL034386, AC004686, AL031659, AL035086, AC006597, Z95116, AL139054, AC004884, AC007051, Z95115, AC004066, AL008723, AL049758, AC006123, AF111170, AL021546, AL022326, AL121657, Z98047, AC007533, AC005377, AC005516, AC004929, AC007030, AC002994, U80017, AC004881, AC006011, AP000356, AC009516, and AC004773.
HCFMZ90	9315	922112	1 - 867	15 - 881		AA099896, W39462, W93311, AA704134, AA102091, AA934684, AA570036, AA973597, AI984459, AA503779, AW073912, AA808602, AA149171, AI984559, AA832230, AA374289, AA651931, AI826677, AA149172, AA715137, W44955, AA046081, and AI377362.
HCFMW71	9316	920506	1 - 631	15 - 645		AI923217, AI814569, AI804682, AI762903, AI804663, AI143304, AI082030, AI139520, AI911904, AW274978, AI183410, AW450838, AI216343, C15320, W93273, AI918971, AA680119, AI823928, R92413, W93272, R92414, T96093, AI216344, T51116, T96094, T51024, AI422647, AI869077, R42713, C00216, AI741425, AI936703, and AA197141.
HCFMU01	9317	916695	1 - 548	15 - 562		AA736920, AA731293, AJ243231, and AI369520.
HCFMP46	9318	463278	1 - 565	15 - 579		AA243868, AA455601, N53291, AA678242, and AW363661.
HCFMO47	9319	881505	1 - 357	15 - 371		AF131284, and AB021227.
HCFML02	9320	920349	1 - 613	15 - 627		AW207866, AI199278, U63312, and U81833.
HCFMJ37	9321	955281	1 - 644	15 - 658		H17763, AL038768, AL035739, AA084554, R52491, H16532, AI750581, AI903894, R21494, Z41981, R13337, AA322574, AA448043, T26420, AA461375, AI903843, AI792383, and AF161445.
HCFMH46	9322	719113	1 - 342	15 - 356		AW239548, AW373232, and AA325059.
HCFLY85	9323	909182	1 - 508	15 - 522		AI340241, AI740877, AA262686, AI949440, AA011068, AA011069, AA281890, AA283910, AA527101, AA250824, AI340240, and AA255646.
HCFLY53	9324	727465	1 - 616	15 - 630		H93046, AA897108, AI652046, T88896, N68615, AA761626, and Z82188.
HCFLY08	9325	959620	1 - 926	15 - 940		AA485570, AA485409, AI458623, R22065, AA639708, AL134139, AL031678, AC004491, AC004985, and Z99716.
HCFLV30	9326	692781	1 - 448	15 - 462		T89518, N91297, R05742, N78236, AA281577, AA505098, and AA282794.

HCFLT86	9327	785560	1 - 546	15 - 560	AA002042, AA001671, AA001672, AA694015, AC009263, and AR068552.
HCFLM03	9328	850403	1 - 488	15 - 502	T64674.
HCFLL03	9329	850406	1 - 823	15 - 837	AA984238, AA525888, and AA525391.
HCFLK10	9330	964792	1 - 760	15 - 774	W31316, AA019148, and AC004706.
HCFLB24	9331	502414	1 - 421	15 - 435	AA568314, AA610433, AI090334, AI871691, AA629679, AL044339, AA515677, AA846923, AI799421, AI049701, AI368732, AA523833, AA173334, AL039309, AI751191, T08386, AW089016, AI821722, F11421, AI732162, AI557422, AW265688, AI049630, AI821172, AI125167, AA662614, F31811, AA663074, AL046746, AA984829, AI792063, AA706202, AA586646, AA130647, M78021, AA862029, AA229988, AW272640, AA610255, AA368012, T48809, AI130709, H96146, AI536858, AW089950, T41134, AI457389, AI537995, AI719142, AA158549, AI814682, AW190277, AI636734, AA564682, F31867, AI291439, AA524846, AW023111, AA481760, AA654482, C06028, AI302156, AA020882, AI054339, AA715351, H24957, AA728861, AA807704, AL079734, AI564301, H67064, AA878492, AI370170, AA557945, AI802526, AI783911, AI671077, AI114494, AL134332, AW166920, AA856817, W63553, AW151935, AI160786, AA434078, T17332, AA384064, AA599080, AW188742, AA323085, H40478, AA371580, R70883, AW419389, H43183, AA368329, AA569089, AI907046, AA126635, AI342677, AA598663, AI342786, AI300413, AW148775, AA326330, AA371410, AA102737, R83585, AW381823, AI376454, AA828463, D51877, H54601, T65895, AI431513, H58393, C18779, F08866, AW162750, AA595504, AI301373, AI929796, AA702618, AA357878, AA315361, AC005015, Z93016, AC005081, AP000512, Z83844, AC004458, AC004796, AC006966, AC004033, AC005189, AC006946, AP000547, D84401, AL035400, Z95116, AP000558, AP000501, AL139054, AL049776, AC005102, AL031666, AC002477, AC005519, AL031055, AC003070, AC005180, AL031281, AC005088, AC005529, Z98200, AL008725, AC003950, AL031311, AL021391, AC005089, AL034429, AC004884, AL136295, AC002301, AL031432, AC002312, AC007376, AC002300, AJ003147, AC003692, AC004815, AL096701, Z95115, Z68277, AC002425, AF111168, AP000067, AC005702, AL034417, AP000557, AC005046, AC005500, AL049869, AC004686, AL022476, U91326, AL008582, AC002550, AP000503, AL031587, AC005412, AC005280, AC005911, AC006251, AL031230, U85195, AC006241, AL049694, AL049636, AL109839, AL022329, AF134726, AC009516, AL109827, AC005193, AL031681, AC002565, AC002400, AC007386, AC005049, AL031280, AE000658, AC004650, AC004905, Z68870, AC004216, AC004791, AC005197, AC005332, AL031228, AC000353, AF030453, AC006064, AC006511, Z98304, AC007842, AC005520, AC002357, AC005839, AL050348, AC005094, AC002351, AC005696, AC005800, AF001549, AC005484, AC008009, AC002039, AC004953, AC005736, Z93930, U96629, AL020993, AC000379, AC006132, AF047825, AC004832, AP000065, AF196779, AC005209, AL034555, AP000116, AC003101, AC007546, AC004881, AC007160, AC006538, U82828, AP000553, AF196970, AP000689, AP000210, AP000132, AC004659, AL035458, U80017, AL121825, AF064861,

						Z99496, AC007686, AC006600, AL049538, AL033397, AC004890, AC005486, AC005598, AC004883, AC006211, AC006285, AC005324, AC005545, AC004000, AB003151, AC006139, AC002430, AC005972, AP000359, AC002544, AC003071, AC004876, AC004966, AC002563, AC005796, AC005899, AC003042, AL109802, AC005781, AC002418, AL031680, Z93241, AL121658, AL022238, AC003982, AC005231, AC005476, AC005619, AC005932, AC007384, AC007192, AC006942, AC010205, L78810, AL109865, AC002996, AF003626, AC002492, AC004386, Z97054, AC003108, AC006275, AC004491, AL021394, Z93017, AL080243, AL133353, AC005295, AL049553, AL008722, AC006130, AC005300, AC003110, AC005225, AC002350, AP000510, AC007014, AC004253, AP000049, AC005363, AL049780, AC005921, Z98044, AF111169, AL022721, AF109907, Z93023, AC005006, AC002470, AP000514, AL049709, AC020663, AC004099, AC004859, AC000026, AC007057, AL035405, AL031728, AC005625, AC005920, AC007637, AC009263, AC006121, AL049779, AL009181, AC000025, AL049552, AF001550, AP000311, U47924, AC005288, AC007371, AP000555, AL035684, and AL133382.
HCFDD43	9332	779327	1 - 216	15 - 230		AI826505, AI810842, AI970815, AW236631, AI400419, N66238, AA035566, and H96744.
HCFCV32	9333	850413	1 - 528	15 - 542		AL119497, AA362532, AC007425, AC004953, AP000311, AP000193, AC006014, AP000117, AC005251, AL080243, AC007999, AC006071, AF196969, AC005488, AC005659, AC004841, and AC002349.
HCFCP77	9334	772256	1 - 366	15 - 380		AI765256, AA806370, AA836325, AI590659, R39398, AA411920, AI807770, and T10620.
HCFCM75	9335	850435	1 - 453	15 - 467		AA513181, AA513141, AI917156, AA491814, AI754955, AI198376, AA714453, AA652764, AA581903, N25296, AI281881, AL133723, AI367497, AI061334, AW088058, AI246119, AW276435, AI298710, AI358343, AW301350, AW303196, AW274349, AI471481, AI357288, AA837677, AW057877, AL046409, AA515051, AA525190, AI610159, AW300625, AW338086, AI284640, AW406447, AI801600, AI624698, AI344844, AW166815, AA448231, AA452563, AW193432, AI287651, AI379719, AW303876, AL119984, F36273, AI350211, AA252763, F37169, AW419262, AW102955, AI431303, AA338486, AI375710, AI963720, AI279165, AI148277, AI580652, AW162489, AW270270, AI860020, AI613280, AI890923, AI610376, AI688846, AI053672, AW193265, AA503258, AW276817, AA557686, AI796627, AW104748, AW022379, AI355206, AW168342, AI830390, T40617, AW276827, AW162049, AI929531, AL041706, T08638, W95841, AI471543, AI887483, AI049634, AI049722, AA451612, F18974, AA340747, AL119691, AI697208, AI144330, AW029038, AI653886, AI469172, AA747472, AI814735, AI708009, AI566794, AA643962, AA302963, AA649642, AA810318, AL043721, AA348311, AI266576, AA350859, AI358571, AA917683, AI339850, W07122, AA229814, AI499938, AA610491, AI962050, AI251002, AA594145, AA229931, AW151896, AW008317, AI334443, AA720702, AI674873, AW339568, AI345654, AI133636, AW261871, AA664407, AI619997, AA225155, AA551575, T07451, AI886164, AI305547, AI249997, AI633007, AW080134, AL120687, AA608616, AA062722, F03097, AA364224, AA653618, F30933,

				AW088202, H86301, AA452744, AL038474, AI291268, AW341892, AA134367, AI291124, AI625244, AW406659, AA177061, AL043756, AI287451, AI357551, T06828, AI341664, W79504, AL120674, AA713815, AI252554, AI937850, AI567674, H70615, AA133986, H37777, AI446464, AA719805, AW021583, AI537955, AW440836, H64765, AI828738, AI904894, AW438643, AW302013, AI889923, AL041733, AA101626, AA810370, N71930, R91994, AW265385, AI824562, AI133164, AI289067, AI270117, AW406162, AA758934, N26137, AL138265, F18638, AI951863, AW265393, AI193007, AI561255, F29702, AA113186, AA099892, AI367975, AI343137, AI457397, AI281697, AA664535, AI754658, H85616, AL120269, AI866908, AI732186, AI371070, AA532877, AA827981, AI471464, AI340453, AF150152, AI623898, AI434311, AI273185, AW238542, AA133333, AA553465, F33121, H72402, AA598586, AA488395, AI564454, AI469003, AI679782, AI053790, AA630030, F10924, T03772, AA843450, AA514737, AW265009, AL079812, AC006001, AP000359, AL117258, AL049829, AC009405, AC010382, AL021068, AC005297, AL021368, AC000022, AL035423, AL121754, AF164343, AC004891, AL049588, AL049780, AC007055, AC006120, Z84487, AL049759, AC007214, AL049836, Z83845, D87675, U85195, AL034402, AL049562, AL109733, AF117829, Z85987, AE000658, AC004519, AC002422, AL049569, AP000567, AC010168, AL121871, AC009501, AP000959, AC005274, AC002038, AL024505, Z80899, AC005922, AC004804, AL109939, AC005301, AC009509, AL109837, AP000548, AC005736, AP000689, AC005722, AC004140, AL031277, AL031280, AL009179, AC007227, AC007878, AJ006996, Z99716, AC004963, AC002418, AC007043, AP001068, AC002375, AP001170, Z93016, AC005771, AC004053, AL109654, AC003684, AC005730, AL022328, AC006207, AL121658, AL132800, Z84480, AL008718, AL008722, AL049766, AC006016, AC009479, AC010072, AL023875, AC004070, U85198, AC002310, AB003151, AC006254, Z92542, AC006222, AC006371, AL049712, AC006241, AC005153, AL121603, AC005102, Z98046, AC004386, AC005548, AC004855, AC003087, AC005529, AE000661, AF095855, AC002994, AC005969, AC004966, Z82216, AL109753, AL024509, AC004629, AC005527, Z80771, AC004531, AL135744, AC007262, AJ011930, AC003982, AC005839, AF165175, AL035494, AC007792, Z84814, AL035416, AL049554, AC011604, AC003003, AC004815, AC003986, AC002463, AL022315, AL035249, AC007968, AC008109, AL031670, AC006210, AC005666, AC006946, AB023054, AC006996, Z83821, AF114156, AL020991, AC005829, AL049745, AC005519, AL022725, Z84469, AC007358, AC005295, AC003951, AC004000, AC007388, AL078602, L78810, AL034369, AC004019, AL121757, AL023799, AL109662, AC011362, AC005632, AC007686, AL136297, AC008079, AC007540, AC004895, U91319, AL034449, AC004583, AC005213, AC006343, AL078612, AL022161, AC007551, Z93930, AL049699, AF200465, AJ239322, AC005188, AL031846, AL109984, AL049835, AL049743, Z83846, AC005261, AC006160, U92032, AC002301, AC006576, AC004914, AL078477, AP001037, AC007066, AC005081, AL121653, AC004502, U07000, AC007225, AL050308, Z75741, AC005562, AC006157,

					AL031230, AC010175, AC002430, AL031650, AC005379, AC000025, AC002036, AC005692, Z97206, AC004081, AC007064, AC005535, AC004485, AP000501, Z97055, AF042091, AL021367, AC007384, AC004527, AC007298, AC000385, AL096861, AC006277, AC004884, AL133500, AC005244, AL022396, AL031673, AL034384, AC007421, AC006480, AC006026, AC002128, AC010849, AL033397, AC004685, AL121825, AD001527, AC004949, AC008018, AC005701, AC005620, AC002412, AC005598, and N25671.
HCFCK25	9336	494159	1 - 529	15 - 543	AL042420, AL134524, AI590906, AI357823, AI284126, AA129746, AI792133, AI110844, AA632757, AI791913, AI961983, AI417469, AI923052, AW303872, AI369580, AI343169, AI358712, AL043351, AL037632, AL118573, AA167055, AC008115, U80017, AC000052, Z93930, AF196969, AC004019, AL021397, AF134726, AC004878, AL031283, AC002400, AC004522, AL022322, AC004765, AC006064, AL139054, AC008101, AC000134, AC007686, AC002519, AF190465, AC005288, AC002316, AC009516, AC005529, AC006001, AF129756, Z83844, AL135744, AC005484, AP000030, AP000553, AL031284, AC004876, AL050348, AC002470, AC004963, AC006277, AL023807, AP000558, AL022320, AC005180, AP000251, AP000008, AC000025, AC005755, AL031848, AL035681, AC007066, AC005488, AC003982, AC005086, AC002425, Z99716, AP000248, AC004832, AL022476, AL020997, AL031311, AC004922, AP000131, AP000209, AP000691, Z93017, AP000704, AP000493, AC005295, AC007371, AP000692, AC005102, AL035071, AL021393, AC005841, AC016830, AC009247, AL096774, AF053356, AC004967, U91321, AC006468, AC000353, AL021154, AC006965, AC002369, AC005786, AC005837, AL049874, AP000133, AP000211, AL050341, AC002350, AP000555, AL049760, AB003151, AL031295, AC004812, AL035423, AC009044, AL031680, AC002091, AC005015, AC003029, AC004217, AC004859, Z83822, AC005914, AC005736, AC005519, AC004598, AC004991, AL031602, AF205588, AC007537, AE000662, AC003102, AD000092, AC003101, AL009181, AC010206, AC007546, AL049589, AC004638, AC005514, AC005215, AC002544, AL049795, AC002115, AL021155, AL096791, AL031228, AP000088, AC007919, AC016831, AC006211, AF001549, AC002559, AC006013, U62293, AC007226, AC005527, U91323, U63721, AC005696, Z95113, AL049779, AC006312, AL022315, AL080243, AC004656, Z98051, AP000210, AP000132, AJ246003, AC007666, AC002984, AL022330, AC005821, AL035659, AL022237, AL021977, AC006130, AC004821, M63796, AC006014, AC005067, AC005274, AC005971, AC005666, AC005588, AP000510, Z97630, AC002301, U95740, AC004999, AC005071, AL035458, AC004230, AC005399, AL034429, AP000140, Z73417, AL035249, U91326, AC006117, AF111169, AP000104, AC005778, AL034417, Z98752, AP000556, AC005412, AC010205, AL031659, AJ003147, AL050321, AL121603, AC007842, AL031390, Z93241, AC005844, AP000112, AC006538, AC006101, AF118808, AC004000, Z98048, AC005480, AP000116, AC005081; AC005291, AF109907, AC008009, AC007425, AC005952, AL096773, AL035462, AF038458, AC007055, AC005031, AC007192, AC004858, Z97056, AF196779, AC004491, U91322, U07562, AL096712, AF217403, AL008730, Z85987,

HCFCG23	9337	850426	1 - 235	15 - 249	AC004659, AC005231, AC004531, AC005057, AC007193, AC004686, and AC005003.
					T96408, AI081046, N80094, AI269862, AI567582, AW163823, AL119791, AI538342, AW129271, AI559872, AI538270, N99092, AI279925, AI922561, AI784230, AI866573, AI500514, AI570966, AL046463, AW161156, AI254727, AI699011, AI572717, AL041772, AI358701, AI539800, AW059828, AW327393, AI432040, AI859464, AI568138, AI419650, AL041220, AA658033, AI540458, AI815855, AI499986, AI685211, AI500523, AL038605, AI581033, AI698427, AW002342, AW152000, AI590423, AW172723, AI445165, AI699255, AI335208, AL110306, AW406745, AW131999, AW148758, AL040827, AW161579, AI929108, AW151714, AW088903, AI689420, AL079794, AI922550, AL036638, AI345416, AL036214, AI345612, AL041150, AW059713, AW029263, AI927755, AL079963, AI863191, AI537261, AI620284, AI241923, AI863321, AI677824, AI445992, AI872064, AI445990, AI345415, AI624293, AA983883, AL036673, AL045163, AI521005, AI434741, AI539028, AI866770, AI696626, AI433157, AI817523, AI702073, AW088899, AI612750, AI251221, AL036772, AI554343, AL036396, AW162071, AL039086, AL036403, AA908294, AW089275, AA911767, AL120853, AI623941, AI500061, AI874151, AW051088, AI890907, AW087901, AI538764, AA641818, AI633125, AI696819, AI698391, AI539153, AW087462, AI538564, AI801325, AI915291, AW152182, AI355779, AI312399, AW020095, AI582932, AI872423, AI284517, AI923989, AI500706, AI364788, AI611743, AI783504, AI868931, AW149925, AI521560, AI889189, AI500662, AI345396, AI345745, AI888621, AI473536, AI589993, AI866469, AA502794, AL119457, AL046595, AI888661, AI873644, AI280670, AW073697, AA807088, AW079572, AI590686, AI859991, AI884318, AI587606, AI783861, AI468872, AI923357, AI336575, AI280661, AI569328, AW238688, AI349964, AW088793, AW193203, AI567360, AI491805, AI680498, AI537617, AI919345, AI922577, AW130863, AW129230, AI698401, AI471361, AW081255, AA830821, AI860003, W74529, AL119399, AI251830, AW081231, AI648567, AA693347, AW149876, AI805638, AI366549, AI799195, AI866082, AI636719, AI470293, AW023859, AA579618, AI620093, AI539771, R40432, AI566630, AI573026, AI866510, AW162189, AI866608, AW022699, AI636619, AI349645, AI805688, AL038565, AW087938, AI249877, AW083804, AI335426, AI348777, AW191959, AI343059, AA848053, AL048323, AI365256, AI367210, AI345347, AL045903, AI434453, AL037582, AI624529, AI345677, AW085786, AI886415, AL037602, AW265004, AL048340, W45035, AI349933, AL038564, W46547, AI677797, AI345608, AW162194, AI683492, AW238730, AI348897, AI857724, N98606, AI251205, AL037558, AW191844, AI765469, AL037030, AI249946, AI961589, AC006197, AL031984, AC004987, AC006112, Z98949, I48978, AL133665, Z72491, I48979, AF185576, AL117460, I89947, A08913, AC006039, AL137533, AL080124, A08916, AF026816, AC009501, AL008637, Y11587, A08910, A08909, I42402, I09499, AC004554, U95114, AR038854, A08912, AL110280, I89931, A65341, AL050172, AF090901, AF106862, AL133104, I49625, AC007172, A08908, AL049382, AF065135, AJ012755, E06743, AF139986,

						AF078844, I33392, AF090903, AF125949, AL137300, AF104032, AC004485, AL050024, AL110196, X62580, AL080127, S78214, AL137556, A93350, AL133077, AF158248, A93016, AF119337, A18777, X82434, AL133113, AC016027, AF067728, AL133558, Z82022, AF153205, S68736, AL050393, AL133565, I00734, AF090934, Y16645, AL049938, AL137459, AL096744, E00617, E00717, E00778, AL133568, AL133014, AL137294, X98834, AL133560, AF111112, AB019565, AL080074, AF113690, AL133067, A65340, E15569, AL122121, Y11254, AL122098, AF113676, AL117432, AF113013, AF067790, AR013797, I26207, AJ000937, AR000496, U39656, AL137271, AL133081, AL137550, AL110221, S76508, AF030513, Y07905, AF032666, X83508, E12747, U49434, AF162270, AF118094, AL049466, A77033, A77035, AF087943, AL049430, AF113699, E02349, AL122111, AL117416, AF111849, AL122100, Y09972, AF125948, AF177401, AL122118, AF106657, A12297, X65873, AL137292, AF008439, A08911, X72889, D83032, X06146, AL080060, AF028823, AL133080, AL137538, AL117649, X92070, AL080137, AL133072, AL122123, U88966, AL137463, E02253, A08915, AF079763, AL137529, AL050146, Y10080, U35846, AL110222, A03736, AF113691, AF081197, AF061943, AF081195, and E03348.
HCFCF76	9338	973808	1 - 636	15 - 650		Z99396, AW392670, AW384394, AW372827, AL119443, AW363220, AL119497, AL119483, U46341, AL119335, AL119319, AL119457, AL119324, AL042975, AL037526, AL042965, AL119484, AL119363, AL119341, AL119391, AL119355, AL119396, U46351, AL119522, AL119496, U46350, U46349, AL119418, AL042970, AL042433, U46347, AL119444, AL134518, AL134538, AL043011, U46346, AL043029, AL037205, AL119439, AL119488, AL042995, AI142139, AC006947, AR060234, AR066494, A81671, AB026436, AR054110, and AR069079.
HCFCC10	9339	964782	1 - 493	15 - 507		AI637997, and AI634156.
HCFBX86	9340	844884	1 - 812	15 - 826		AC005630.
HCFBQ30	9341	692787	1 - 538	15 - 552		R53757, H86858, R92462, AI032557, and AJ238093.
HCFBM75	9342	766599	1 - 440	15 - 454		H73824.
HCFBM41	9343	711631	1 - 760	15 - 774		H48509.
HCFBK28	9344	706243	1 - 399	15 - 413		AI052103, AA443680, R73756, and AL035593.
HCFBK04	9345	925601	1 - 729	15 - 743		AI479244, N62936, AW043736, N62922, AW070399, AI439134, AI087958, AI923614, AI042445, AI141286, AI240322, AW139229, AI167559, AI142623, AI654168, AW044610, AI370719, AA715102, R70258, AI184401, AA862632, AA053035, AA418550, and AA418648.
HCFBI51	9346	670066	1 - 534	15 - 548		R22358, R73854, T19084, AJ242972, and AJ242971.
HCFBA94	9347	698647	1 - 588	15 - 602		AI692432, AI206257, W72986, W76185, AI797925, AI498429, AA888959, AI139097, D62001, AA506656, R14258, N49612, AA897171, and AC009464.
HCFAZ12	9348	970609	1 - 333	15 - 347		AW419262, AI284640, AW021583, AI246796, AA831375, AI298710, AA649642, F36273, AI049722, AL041706, AA513141, AI446464, AA669251, AI707788, AW302013, F33121, AW193265, AA513181, AI827234, F33566, AA557686, F25276, AA441788, AA100599, AA084070, AA493708, AI434695, AA551575, AI624698, T40077, AA586458, T47588, AI144055, AI250019, AI291124, AI564185, AW131034, AI937850, AI266133, AI245679, AA340747,

					AI015152, AA618141, AI921296, AA514819, AI368256, AI148245, AI572560, H70615, AA127486, T40617, AA572975, AA365302, AI355224, AA649705, AA825357, AI471481, AI439360, AA299115, AI291268, T07451, AA640986, AA078831, AA488746, AI358343, AA169777, AI133164, AA244286, AA515909, AA491814, AI821028, AI821279, H96823, AA469451, AA161095, AA977743, AI040313, AA720702, AA602951, R93061, AA973803, M87917, U14708, AC005914, I51997, AF108024, AL035072, U02054, U02050, AC000025, AC005527, AC006026, AF077058, AC005529, AP000512, L35531, AF207550, S77605, U02048, AC006039, AB023051, AC002059, AL109865, AL031846, M87916, AL035659, AC004447, AL109628, Z82244, AL035681, U67827, AC005578, Z22650, Z46940, AC006285, U91321, AP000555, AC005944, AC003038, AC020663, AC005015, AP000349, AC005212, AL035413, U32576, AC000094, AC004638, AC003098, AC005023, AL022476, L48038, AL020995, AF003626, AC002418, AC007162, Z83840, AC002133, AL021391, U50871, AL035458, AL136504, AL096701, AF029308, AC000353, AC004386, AC004686, AF045555, AC007308, AL078460, AC002492, AC004854, AC002563, AP000557, AC006117, Z86090, AC005081, AL031681, D00591, AC005911, AC007686, AC005775, U67826, AC005913, AF053356, AC004962, L47334, AL021918, AC002036, AC002377, AF124523, AC005730, AC007565, M19045, J03801, E01888, E02193, AC008115, U95742, AC002470, AC002524, AL096791, AC006344, AC007216, AL109939, AC010072, AC006449, AC004152, Z69918, AC004963, AP000352, AC004884, AC005755, AC005480, AF190465, AL021940, AL031258, AC009891, M37551, AC007999, AL020997, Z98882, AC000026, AL031293, AF090944, AC002126, AL022323, AC004896, AL023882, AC002369, AC005940, U15422, AC003663, AL031650, Z68756, AP000556, AC005660, AC004593, AL121825, AC000085, Z99571, AL031289, Z98051, AL034430, Y07848, AC006040, AC007751, AC006441, AC007191, AC002477, AC007536, AC004646, AL031591, AC003030, AC004751, AL031311, U67825, AL034451, AC012599, AC005028, AL033525, AC007151, Z82195, AF126403, Z81450, U34879, AC002056, AL079340, U62317, AL133448, AC007911, AC006538, AL136297, AC004699, Z94055, AL021978, AC016025, AC007387, AC005202, AC005338, Z84572, AC004967, AC006111, AC002072, AC002367, AC005740, AC004647, AC016026, AC005379, AL031432, AP000705, AC005229, AL135744, AF041427, L81576, AJ003147, and AL078640.
HCFAZ07	9349	849823	1 - 522	15 - 536	AA155821, AA608744, AI879998, AW168112, AI052703, AW104051, AW157334, W84527, AA648295, AW192895, AA861283, AA947742, AW057835, AI582368, AI193965, AI300565, AW009823, AW029295, AI348116, AA708118, AA577690, AA101195, AI016610, AA527861, AA480279, AI452699, AA669337, AA760760, AA744919, AW130090, AA831711, AI057288, AI494111, AI800064, AI862854, N62094, W55920, AA043251, AA001852, AA292750, AI275625, N93127, AW007135, AW272692, AA160010, AW166814, AI198852, AI271553, AA484277, AA025382, AA971631, AI346774, N50975, AA088421, AI130684, AI354226, AA453035, AA984913, AA668696, AI090673, AW264660, AA152365, W15314, AA807549,

						AA187227, AI521457, AI969402, AA722831, AA764824, AA788597, AA633795, W67807, AA928577, AA565588, AA026016, AW075660, AI886794, AW439109, AI797422, AA010759, AA284411, AA765379, AA179097, AA741542, AA120907, AA459969, AA586336, AI695507, AI190992, AA028052, AA857371, AI206746, AA131616, T63795, AW020230, AI123351, AA281235, W60465, AA426610, AA780786, AA083357, AI439077, N78325, AI281441, AA568376, W52413, AI826611, N66464, AI370333, AW117628, AA460061, AW439098, AW022530, AA278324, W55919, T47065, AA204925, AA011120, T34888, AI758966, AA491375, W84515, AA292539, AA845300, AA827429, AI074775, T64028, AW438482, AA226936, AA574112, T94385, AI290025, AA460014, AA092473, AA926777, AA621388, AW009092, AA482700, T35591, AA738461, N33952, AI887555, AA147057, AA211143, T52042, T51962, T30133, AI368809, AA142894, AA132330, N58965, AA131382, AA147058, AA480155, N38911, AA732979, AI797801, Z39146, AI566368, AI001836, AI690968, AA525773, AA327661, AA525871, AA525751, AW080274, AW373539, AA991829, AI139106, AI874015, N56031, AA398724, AA665715, AA043590, AA661828, AB030905, U95740, Z84488, AC005841, AL023775, and AB005618.
HCFAF08	9350	959714	1 - 277	15 - 291	Z43308, and F06087.	
HCFAC38	9351	576723	1 - 563	15 - 577		
HBYAB02	9352	971578	1 - 371	15 - 385	AI290084, AW069571, AL045559, AI916323, AI920788, AL037725, AI979070, AA558973, AA805073, AI923608, AI026817, AI400065, AI142752, AI073801, AI983052, AI888249, AI814624, AI954566, AI634706, AI685954, AI826322, N32025, AI523819, AW193468, AA431425, AI471592, AA494404, AI913467, AA975219, AA134828, AW002764, AI435532, AW196856, AW167131, AW020997, AI872178, AW168867, AA953123, AI096566, AW439581, AI274717, AI589346, H29599, AI088270, AA777093, AW196804, AI080172, AW261884, AI654244, AI247070, AI174662, AI368857, AI859769, AI804043, N69326, AI800419, AI077452, AI000904, AA614709, AA932332, AI811787, N51228, AW173627, N67399, AA665721, AA872701, AA630621, W45368, AW339689, AA813724, AA431829, N69549, AA483167, AI167605, R38982, AL040955, AA946853, C15258, AA367583, AW020365, AA470959, AA470492, D60743, AI241864, AA599645, AA504467, AI582507, AI865471, AA908302, AI125505, AW270390, AI251461, AA976144, T90631, AI675925, AI094039, AA868559, AA350318, AI420632, AL044108, AA725887, AA912279, AL043485, AA483807, AA432375, W94957, AI473795, N89726, AI149616, AI677962, AA449963, AA435852, AI439074, AI375050, W94259, AI359458, AI422102, R16090, AI832410, AA350322, AI520933, AI372467, W94673, AW241206, N50917, AA962014, AA962188, T49442, AI076757, D59874, AI383209, AA694588, AI150484, AI954233, T65112, AW002717, AI270073, AA635251, N74638, F09484, H44439, R39314, AA134827, AI445189, W95853, T79742, W95599, W81307, AA729817, AA363740, AW162362, AI126993, C01293, AI203813, AW337288, AI280943, AW087446, AA461546, D61229, AA398843, AA738229, AA938675, C02201, AI783852, AL045344, D56705, D29216,

					AI003102, AW193553, AW051049, AW263449, AW338767, AA194855, R17015, AI187752, AA299747, D56913, N83414, AI074015, W95598, R43379, AI372469, AA372620, AI915250, C14909, AL040146, C15727, AA911490, AI972644, AW193598, AI271716, AF131738, and AL022240.
HBUAG44	9353	716685	1 - 336	15 - 350	AL134194, and AA211828.
HBUAC23	9354	847698	1 - 342	15 - 356	H65948, and AA522538.
HBTAE84	9355	781946	1 - 387	15 - 401	
HBMXU73	9356	953898	1 - 687	15 - 701	AI912940, AI356880, AA768753, R38430, AW026385, AI094990, AA417714, AI521674, AI911847, H17932, AA603061, AA152297, AI469372, AI038106, R65634, N71126, AA602303, N47801, AI445560, H10196, AI566092, AA131931, N39095, N57531, AI537013, AI951484, AI972988, AI141578, N34391, AI867900, AA830221, AA058539, AW057639, AI703292, AI866150, AI393673, AI307808, AI129217, H11742, Z39045, T24056, F01755, F03814, R36084, AI471051, R51266, R42298, H07915, AA412728, F01735, AW170333, and C01600.
HBMXS23	9357	675254	1 - 442	15 - 456	T56858, H47055, AI097490, T48207, H47127, R06541, T48206, and AC000393.
HBMXL78	9358	738763	1 - 451	15 - 465	AA040902, W79933, AI818085, AI831014, AI819405, AI814284, AI570554, AW005883, N92092, AI373828, AA365266, AA705064, AI073849, AA150396, AW081533, N31954, AI078328, F19605, AA688147, N44237, AI814155, AA385643, W78108, AA934651, AA661822, AA448574, AI669184, AA719546, AA594574, W02992, AA035203, W46177, AI304898, AI042436, AI702857, AW300688, W46540, AA724939, N24291, AA862274, H47300, AA989294, H21424, AA935840, AI968456, R44002, W87615, AA302189, R32790, AI468314, H59434, AA156578, R94915, AI868335, AW277188, N69447, N34605, AA903411, AI754560, AA441863, AA449263, AL117548, and AF064084.
HBMXL41	9359	711608	1 - 452	15 - 466	R99651.
HBMXJ70	9360	757328	1 - 443	15 - 457	H64110.
HBMXG10	9361	968055	1 - 362	15 - 376	R13146, and AC006960.
HBMXF73	9362	764551	1 - 463	15 - 477	H71766, and AL050032.
HBMWX13	9363	955208	1 - 435	15 - 449	AI690702.
HBMWS75	9364	767440	1 - 425	15 - 439	R00589, and Z84467.
HBMWR62	9365	754059	1 - 466	15 - 480	AA179886, AI124981, R68627, and AL079296.
HBMWK06	9366	936088	1 - 236	15 - 250	AA608586, and AI863209.
HBMWI28	9367	685443	1 - 375	15 - 389	R11487, AA668261, R12375, and AA905206.
HBMWE35	9368	706034	1 - 645	15 - 659	AA001457, AA015999, and AF062922.
HBMVQ26	9369	546495	1 - 290	15 - 304	
HBMVO41	9370	712565	1 - 440	15 - 454	R60294, and AC005007.
HBMVI33	9371	702683	1 - 405	15 - 419	R18185.
HBMVG85	9372	575418	1 - 208	15 - 222	H08588, AW452797, R61253, AI460322, AI039491, AA416798, AA609458, AI867411, AI631600,

					AI206856, AI015080, AW004016, AI880436, Z41596, AI928117, and AA774212.
HBMVG18	9373	666855	1 - 571	15 - 585	N80648, H82296, H95468, T96215, and AI630703.
HBMVE59	9374	933208	1 - 409	15 - 423	H77697, H77689, H77703, H69186, and AF165138.
HBMVD05	9375	932441	1 - 343	15 - 357	T73358, and AC006947.
HBMUW96	9376	574517	1 - 296	15 - 310	AL078644, and AC011311.
HBMUW85	9377	783416	1 - 612	15 - 626	R51759, AA035757, AA159960, and AF110908.
HBMUW58	9378	574513	1 - 202	15 - 216	AC007539, and AC006560.
HBMUN03	9379	847787	1 - 478	15 - 492	AA824413.
HBMUL31	9380	456760	1 - 549	15 - 563	
HBMUG59	9381	739509	1 - 497	15 - 511	AA429725, and AA281396.
HBMUG23	9382	425961	1 - 605	15 - 619	
HBMUD91	9383	789320	1 - 589	15 - 603	T84888, AA960882, AF051976, and AF144094.
HBMUB13	9384	950984	1 - 555	15 - 569	W01309, AA577113, AW292823, D20298, AI240027, F17130, T30300, AA744372, H75572, AW204120, and AA433861.
HBMTX71	9385	760605	1 - 420	15 - 434	H59274.
HBMTS23	9386	676310	1 - 385	15 - 399	R25927, Z45765, and AL008726.
HBMTR29	9387	847785	1 - 509	15 - 523	AA573319, AA634778, H56345, T92363, AI708233, H56344, T92415, and A90848.
HBMTM67	9388	751907	1 - 305	15 - 319	R24667, AI741100, AI689414, C14069, and AL031681.
HBMTD69	9389	754179	1 - 469	15 - 483	R34775, and AI150382.
HBMTB85	9390	923730	1 - 432	15 - 446	W21033, AI924201, AA766826, AA888820, AI814342, AW001123, AW134874, AI366738, AA670436, AI935359, H42655, AI198343, AA665651, H42654, AF077740, Z97630, and AF093403.
HBMTB34	9391	706024	1 - 460	15 - 474	W86935, W86925, and U95626.
HBMSX83	9392	863883	1 - 493	15 - 507	AA256753.
HBMDS02	9393	920096	1 - 429	15 - 443	AA626212, and Z63877.
HBMDN16	9394	661947	1 - 493	15 - 507	H06534.
HBMDM25	9395	678127	1 - 586	15 - 600	H00140, and AA284312.
HBMDL27	9396	683427	1 - 487	15 - 501	N52474.
HBMDF52	9397	727169	1 - 535	15 - 549	T63944.
HBMDD72	9398	879813	1 - 407	15 - 421	D58283, D80268, AW178893, D51022, C04682, D80212, D80188, D80064, C14014, C14389, H67854, AA809122, F13647, D59653, D51759, H67866, C15076, D80195, D80439, D58246, D81030, D51423, D80251, D57483, T11417, C03092, D80258, D80157, D81026, D59859, D80269, D80022, C14331, D80014, D80166, D80366, AA305578, D59889, C14973, D80196, D59467, D59619, D80133, D80247, C14227, D80210, D51799, D59503, D80391, D80164, D59275, D80248, D80240, D80253, D80045, D80038, D50979, D80219, C06015, D80043, D59787, D80227, D59502, D50995, AA305409, AW375406, D59474, D59610, D51221, D81111,

						D59551, D59317, D80522, D51103, D59927, AW179332, AW360811, D80024, C14046, AI535686, D80193, D58101, D80302, C05763, AA514186, AA514188, AW178906, AI525912, AW369651, D45260, AI525242, AI557774, AI525235, AI557751, AI525920, AI525917, AA514184, AI535959, AI525215, AI525227, AI525923, AI525237, AI525925, T11191, L81613, A87015, AR008278, A84916, AB002449, A62300, A62298, I14842, AB028859, A82595, AR054175, AR060385, AJ132110, AR008277, AR008281, AR018138, AF058696, X68127, X67155, D88547, AR016691, AR016690, and U46128.
HBMCZ30	9399	692733	1 - 516	15 - 530	W38346.	
HBMCT24	9400	677209	1 - 338	15 - 352		
HBMCT09	9401	625627	1 - 653	15 - 667	R78567, R22348, AI138749, AI432160, and AI378357.	
HBMCS92	9402	792736	1 - 425	15 - 439	T89785.	
HBMCS55	9403	731802	1 - 597	15 - 611	AA252232, H30735, H30819, and AF085888.	
HBMCR25	9404	678164	1 - 988	15 - 1002	AA766345, AA258762, AA258882, and R87385.	
HBMCQ95	9405	888393	1 - 359	15 - 373		
HBMCG84	9406	783043	1 - 407	15 - 421	T80409.	
HBMCF20	9407	646279	1 - 595	15 - 609	AA160470, AA594945, AL047220, and Z98884.	
HBMCB55	9408	731800	1 - 359	15 - 373	R09103.	
HBMBX72	9409	911168	1 - 887	15 - 901	AA077388, AL043009, AF039185, AW243793, AA974503, AL079869, AL044339, AA078338, AL079812, AI567674, AW008212, AI499938, AL039996, AI732120, AA908687, AW102955, AI679782, AI582769, AL041706, AA563818, AA255853, AW406162, AA287570, AA680243, AL044340, AA884598, T74524, AI356440, AI110760, AL121235, AA578590, AL038842, AI799642, AW089016, AA349366, AA806796, AI635279, AI434695, AI917156, AA643434, AI053790, AW302711, D82290, AI144081, AI313166, AW276586, AI708009, C06151, AW301906, AW342042, AL044940, AL048925, AW302753, AC004878, AC005081, AC004895, AC010205, AC004134, AC003682, AC005488, AC002350, AL023553, AC006057, AL022165, AC008101, AF053356, AC003104, AL080243, AL121653, AC005783, L78810, AC005015, AL139054, AC008079, AL133448, AC005088, AC005399, AL034423, AP000557, AF001549, AC007731, AL049869, AC007371, U85195, AF196779, AC004882, AC004814, AC005520, AL022322, Z99716, AC002563, AL121603, AE000658, AC000025, AL050318, AC004883, AL022238, AL022721, AL096712, U95740, AC007055, AF134726, AC004796, AC004815, AC004217, AC006130, AC005940, AC005531, AC006511, AC006014, AC006571, AL096791, AC007919, AC007227, Z97630, AC004000, AP000350, AL049712, Z84487, AC007066, AC002404, AF088219, AL050307, AC009247, AC006285, AC002115, AL008582, AC000026, AC003007, AC004019, AC004832, AL035458, AL135744, AF165926, D87675, AL080242, AC005500, AC004542, Z98051, AL021154, AC002543, AC002303, AL022323, AP000690, Z93241, AC005606, AC005067, AC007324, AC004033, U80017, AC004638, AF111168, AL049776, AC006006, AP000045, AC006111, AL022311, AC008040, AP000338, AC006251,

						AL050341, AC000353, AC002477, AC004963, AP000502, AC007225, AC000070, AC007021, AC004876, AL034555, AL049795, AC002425, AC006080, AC005288, AL022476, AC009731, AD000092, AC006088, AP000359, AL022336, AL035405, AL008718, Z84466, AL034420, AL033392, AC004675, AL133243, AC005409, Z97054, AL117258, AC005527, AC005412, AC007666, AP000216, AC005821, Z68276, AC004858, AC005049, AC006064, AL031311, AC002996, AP000692, AL096703, AC002395, AC006241, AC005763, AC005632, AC007298, Z98941, AC000159, AL035079, AC006013, AL049759, AF129756, L78833, AC003962, AP000555, AC006160, AB023050, AP000504, AL109627, AJ246003, AC005005, AC005519, AC009516, AL035659, AC005562, AF030453, AC000035, AC005300, AC005291, AC005231, AL023807, AC006501, AC002316, AC005180, AL049709, AF064861, AC007536, AC004913, AC005971, Z95114, AL021453, AC005722, Z98036, AC004531, Z99943, AC004491, AC006312, AP000030, AC006023, AC005736, AP000114, AP000046, AL031846, AL109984, AF111169, AC006146, Z85987, AC000003, AC005041, AP000351, Z95152, AC005914, AC007686, AC005703, AC005037, AC004821, AC005602, AP000503, AC005332, AC004967, AC004813, AP000501, AC005837, AC006449, AC004771, Z83844, AL022318, AC005954, AL023803, AC004893, Y18000, AC007690, AC007687, AC005777, AC002312, AC002314, AL049569, AC003101, AC008044, AC005796, AC002565, AC002126, AC002375, AC005620, AC003982, AP000065, AC005920, AL031291, AC004841, AL049636, and AL049872.
HBMBX64	9410	746633	1 - 599	15 - 613		R64027, R39393, and AW262338.
HBMBX55	9411	668981	1 - 660	15 - 674		W02418, AW374577, H06101, AA478509, AA149906, N58721, T05803, AW374575, AW374603, AI038699, AF044588, and AR032001.
HBMBU52	9412	973805	1 - 541	15 - 555		AI962282, and Z98050.
HBMBN85	9413	783520	1 - 283	15 - 297		W79516, AA976168, AA344920, Z84487, AC009509, AC007546, AF031078, AF030876, AC004087, AC005520, AC007216, AC005479, AL035667, AC004531, AL133448, AC007993, AL121655, AL031584, U95742, AL031575, AF165926, AC005081, AP000553, AC005823, AL109984, AL133371, AL096701, AC004883, AC019014, Z99716, L44140, AC005837, AL132712, AP000030, AC004659, AL023807, AC005529, AC005231, AC006501, AC005015, AL031311, AP000555, AC005011, AF053356, AL022313, AP000134, AP000212, AF111168, AC007899, AC007687, Y10196, AC005225, U80017, AC000120, AC005037, AC006947, AL132826, AP000501, AC004263, AL034395, AF207550, AL078477, AC005512, AC006064, AC002476, AC004890, AC004410, AP000337, AC002470, and L78833.
HBMBI49	9414	723094	1 - 520	15 - 534		H83282, and H61030.
HBMBF89	9415	912789	1 - 938	15 - 952		AI524149, AA214070, N32863, AW269871, AI337580, AI567436, AI797310, AA913630, AI674495, AI201224, AI004609, AI685959, AW316868, AI374695, AW130375, AI420705, AI363214, AI201959, AW025086, N57161, AI718664, AA738168, AI991056, AI079888, AI923956, AW370538, AA557806, W88855, AI984189, AI376436, AI240957, AA780294, AI868941, W46418, AA350784, W88536, H57851, AI202868, T86691, N29741, AI358983,

					T86779, W72654, T86785, AI356251, AW134759, AA761197, T32285, R52494, C00788, AA983316, AI797525, AW135739, AA213524, W49846, AA938126, W76616, AI419595, T86686, AA635708, AI962906, T20097, T30685, H59977, AA565271, AI088829, AW418557, U83525, AA481982, AA482087, AA864361, and Z22819.
HBMBF78	9416	623421	1 - 950	15 - 964	AA683395, W39500, and AA159553.
HBMBE68	9417	879588	1 - 388	15 - 402	AA770612.
HBMBC66	9418	859500	1 - 339	15 - 353	W73386, and AI910369.
HBMBB57	9419	734915	1 - 324	15 - 338	AW080136, AA648683, AI625125, AW193143, AA635976, AI064811, AA935848, AL037910, AA564865, AA627154, AW166653, AI932443, AA501614, AW302709, AA578231, AA491807, AA845804, AI565097, N68677, AI572115, AI302917, AA857381, AI560195, AL041375, AL040054, AA533344, AA515046, AA366716, AL047429, AI769271, AA229935, AI024339, AW028908, AI287706, AA757888, AI539530, AA508873, AI061313, AW020094, AA833896, AW117860, AA833875, AI249688, AC006023, Z84469, AC004019, AC005412, AL121603, AC006487, AP000509, AC004217, AP000512, Z98950, AP000359, AC008101, AC006077, AL035090, AC006285, AP000313, AP000013, AP000155, AC007285, AC005998, AF069291, AF003626, AP000050, AF067844, AC016025, AC006008, AL022476, AC005215, AF111169, AP000117, AL022316, AL022327, AL049759, AL132987, AC007096, AL132985, AF029308, AC004185, AL033527, AC010175, AC004087, AC000120, AC007536, AC002996, AL049829, AC005067, U63834, AL050321, AC001228, Z97876, AC004738, AC005358, AP000036, AL080243, M29929, AL035703, AC009263, AF111168, AC002110, U95740, AC006552, U89337, AC005225, AF165926, AC020663, AC003982, AF134726, AL022238, AC005243, AP000193, Z84487, AL031427, Z84466, AC004675, AC005914, AC006449, AC007226, AP000511, AC005399, AL031985, AC007934, AC006115, AL050308, AC005839, AF196969, U95742, AL023553, AF109907, AC004914, AC006111, AC002105, AL008725, AC005058, AC005191, AC003950, AL022320, AC003029, AC004686, AC004843, AL133163, Z93023, AP000047, AC007216, AC002430, Z83822, AP000432, AL034421, AC007384, AC004834, AC006239, AL034420, AC007664, AL121825, AC006312, AL031846, AF064861, Z86090, AC004875, AL008715, AL049539, AC004678, AC000052, Z85986, AL034423, AC006972, AC005726, AC003037, AC005944, AL008582, AC006146, AC006384, AC004531, AC003690, AF121781, AC005180, AC007649, AP000692, AC006511, Z94793, AL049694, U95743, AL139054, AP000038, AL079305, AC007199, AC007385, AC005089, AP000034, AC002073, AC004491, AC002470, AC008018, AC004893, AC005182, AC002477, AL117694, AL133245, AC005971, AC007324, AC004859, AC007308, AL022318, AF002223, AL034379, AL031282, AC004858, AF047825, AF038458, AC003682, AC008134, AL031597, AC005233, AC002395, AC004458, AP000115, AC004216, AC005632, AL035249, AC002551, AC006501, AC004000, Z82181, AF107885, AC006966, AC005088, AL009179, AF088219, AC006530, Z84480, AC005618, AC008079, AC005832, AC005800, U85195, AC002040, AF190465, AP000502, AC004996,

					AC006318, AL033376, AC005694, AP001052, AC005696, D84394, AC005086, AL022165, AC004841, AC004647, AL049780, AC005207, AC007050, AC007041, AC003664, AE000658, AC004929, AC003663, Z98884, AL024509, AC004967, AC005740, D87675, D28126, U91326, AL023280, AC006084, and AC001231.
HBMBB45	9420	578817	1 - 343	15 - 357	AJ242976.
HBMAC54	9421	930481	1 - 421	15 - 435	AF037641, and AA321292.
HBJNC01	9422	915970	1 - 352	15 - 366	AA737327, and AI433448.
HBJNB52	9423	726475	1 - 484	15 - 498	R93012, and AA856773.
HBJMW95	9424	797604	1 - 805	15 - 819	AA460141, AA460739, AA487420, AA487676, AI620475, AW014765, AA826244, AI807477, AI859817, AI888070, C01748, and AA487462.
HBJMW03	9425	921996	1 - 951	15 - 965	H19011, AA017590, H86398, AA969667, AA055983, and AL009182.
HBJMU53	9426	727987	1 - 458	15 - 472	H10282.
HBJMS40	9427	710880	1 - 371	15 - 385	N55533.
HBJMR59	9428	738615	1 - 622	15 - 636	H72483, AI125256, and C15483.
HBJML90	9429	787320	1 - 433	15 - 447	AI566099, AW027347, AI921989, AA769157, AA722358, N66761, AI696509, AI825693, AA651815, AI933564, D59982, D61092, AA860600, D59981, D61152, AI873970, AA831741, H02809, AA653665, and AL050064.
HBJML80	9430	775435	1 - 451	15 - 465	W17090, and AW022657.
HBJME11	9431	972939	1 - 457	15 - 471	
HBJMC69	9432	754875	1 - 290	15 - 304	N80651, and AC002400.
HBJMA80	9433	777456	1 - 425	15 - 439	H37828, and AA707167.
HBJLX09	9434	625319	1 - 428	15 - 442	T56980, AF178030, and AF147313.
HBJLW74	9435	765352	1 - 398	15 - 412	AA290916, R00373, AW387125, AA449392, AW387122, and AL080141.
HBJLU36	9436	847851	1 - 426	15 - 440	H38564, AC005049, AC005245, AC006014, AC005488, AC006195, AC003043, AF001549, and AC005071.
HBJLR37	9437	849633	1 - 416	15 - 430	AA084033, AA126948, AA126949, AA070285, U67770, X02414, X63389, and AA070164.
HBJLR31	9438	900883	1 - 1440	15 - 1454	C14331, C14429, D59275, C14389, AA305578, D80227, D59859, D80164, D80378, D80195, D59467, D59502, D80038, D80269, D51423, D58283, D80022, D51799, D80166, D80253, D59619, C15076, D80210, D80391, D80240, D80043, D59787, D81030, D81026, D80024, D80212, D50979, D80193, D80196, D80188, AA305409, D80219, AA514188, D57483, D59927, D80366, D51022, D59610, D59889, D50995, D80045, D80248, AW177440, AA514186, D80241, AW360811, AW178893, D80522, D80251, D51060, C14014, D80133, T03269, AW375405, AW179328, C75259, AW179020, AA809122, C14407, AW179023, AW366296, AW378532, AW377671, AW360844, D80268, AW360817, AW375406, AW378534, AW179332, AW377672, AW178905, AW177501, AW177511, C05695, D80302, AW179019, AW178762, AI557751, D51250, AW352171, D80439, AW377676, AW178906, AW352170, AW177731, D80132,

						AW178907, AW178775, AW179024, D80247, AW179018, AW177505, D80134, D58253, D51103, AW352158, AW360841, AW178909, D59373, AW352117, AW177456, AW179329, AW176467, AW369651, AW178980, AW177733, AW378528, AW178908, AW178754, AI535686, AI910186, AW352174, AW179004, D59695, D52291, AW179012, AW178914, F13647, AW378525, D51079, D80157, AW177722, AW177728, T11417, D80168, AW367967, AW179009, D51759, C06015, AW178774, AW178911, AW378543, AI905856, AW352163, C14227, C14344, D81111, C14298, AW178983, D80064, AW178781, AW360834, D58246, T48593, D59503, AW378540, AW177723, AW352120, D59653, D45260, D59627, Z21582, D58101, D80258, AI535850, AW367950, C14975, H67854, C03092, D51097, AW378533, H67866, AI525923, D59317, AA285331, AW178986, T03116, AW177508, C14973, AW177734, N66429, AI525917, D80014, AW177497, D45273, D51213, D51221, D59551, D59474, AI557774, AI525920, D60010, AA514184, D60214, AI525227, T02974, C14957, D50981, C14046, AI525235, AI525242, T03048, AI535961, AI525925, AI525912, AW378542, AI535959, AW378539, AI525215, C16955, AI525222, A84916, A62298, A62300, AR018138, Y17188, A82595, AJ132110, AR016808, AB028859, AR008278, AF058696, Y17187, X82626, D26022, Y12724, A25909, X67155, A67220, D89785, A78862, D34614, A30438, AR060385, D88547, A94995, AB002449, I82448, X68127, AR008443, X64588, AR025207, I50126, I50132, I50128, I50133, U79457, AR066488, AR016514, AR060138, A45456, A26615, AR052274, AR008277, AR008281, Y09669, A43192, A43190, AR038669, U46128, AR066487, I14842, AR066490, AR054175, AB012117, I18367, D50010, AR016691, AR016690, A63261, A85396, D88507, AR066482, I79511, A44171, AR008408, A85477, AR062872, A70867, I19525, A86792, X93549, D13509, A64136, A68321, AR060133, AF123263, AR060382, AR032065, and AR008382.
HBJLF04	9439	614915	1 - 323	15 - 337		AA192415, AI216292, AW151132, AA573503, AA827164, AI207431, AF069506, and AF070643.
HBJLE70	9440	847853	1 - 993	15 - 1007		AI720923, AI628097, AI149416, AI432468, AI038395, AI360839, AA235040, AA010019, AW104170, AI266742, R80513, AA954623, R80407, H81294, AA235207, AA992698, T98403, AA480593, AI352046, AA807246, AA010161, T98402, AW078986, AI572359, R64407, AI547277, and AC004148.
HBJKI77	9441	772000	1 - 683	15 - 697		AI763332, AI744915, W02174, W32586, and AL109627.
HBJKG07	9442	952843	1 - 806	15 - 820		AI739538, AC006140, AB023052, and AP000513.
HBJKF02	9443	919446	1 - 385	15 - 399		AA278175.
HBJKD77	9444	771975	1 - 393	15 - 407		
HBJKD64	9445	746398	1 - 341	15 - 355		AW162288, AI696793, F13749, AI431434, AI537538, AI358089, AW021116, AW157005, AA657835, AA508809, AW328331, AA130647, AI954525, AA992126, AI051037, AI028510, AI751162, AW271917, AI340641, AA728937, AI500552, AI821881, AI821918, AA865262, AA629412, AA829065, AA804925, AI566408, H90844, N67343, AW089589, N23260, H71678, D29500, AL046746, H79308, AL038936, F30251, AI291961, AI887716, AW192065, AI571656, AI309384, AI961536, AA714011, AI279417, AA644320, AI598060, AA669840, AI144036,

					AW302950, AI570943, AA563770, AA371513, AC005412, AL117536, AC009946, Z93930, AL133245, AC004692, AL022313, AL050332, AC000353, AC006236, AC005280, AL031255, AC005726, AC005899, AC004832, AC020663, AL021939, AL035413, AC000052, AC005539, AC004922, AC007344, AC004019, Z82244, AP000270, AC004854, AC005484, AC005996, AP000032, AC006080, AC005874, AF134471, AC005081, AL021453, AP000215, AP000116, AC007057, AL049872, AC006356, AL049757, AC005231, AC007055, M87889, AL035587, AC004167, AC005696, AC005531, U53930, AP000557, AP000558, AC009516, AC006468, AL022238, AC004996, AC005399, AF038458, AL031296, AC006600, AC003667, AC007283, AC005015, U91321, AC004072, AC004534, AC007899, AL021154, AL035667, AL031003, AC007308, D87675, AP000513, AC005800, AC002483, AC004794, AC006064, Z68321, AC005013, L35485, AC008071, AC005962, AC004921, AL121653, AL049780, AC002115, AC000070, AP000503, AC005037, AC007226, AL033376, AL035448, AC002375, AC004087, AC005940, AC004231, AC005046, AL109827, AC002470, Z85987, AC004536, AF134726, AC004963, AC005900, AC005520, AC005620, AC007376, AC005498, AC005089, AC006441, AC002350, AL080285, AC007237, AL031407, Z99716, AC009509, AL034423, AP000049, AL031393, AC004887, AL050318, Z83844, U85196, AC004452, AC005616, AL050341, AP000311, AL008719, AF011889, AF111169, AF196779, Z72521, AC006530, AL034553, AC006512, AC005193, AC005057, AC004150, AL031733, AC005062, AC006277, Z95114, AC005529, AC007731, AC005602, AC006057, AF050154, Z84476, AP000689, AC003682, AC002059, AL008735, AP000090, AC004477, AC006111, AC002530, AP000356, AL133485, AC003665, AE000661, AC007228, AC004890, AL109984, AL020997, AC004253, AC004859, AL022165, AL022163, AC018633, AF195658, AC005192, AC006071, AC004876, AF031078, AL049830, AC005914, AC004263, AL034555, AF030876, AC004687, AC005004, AB003151, AC005229, AC005664, AC005500, AL021395, AC000025, AL034402, AC003690, AC005876, AL022397, AC000097, AC005780, AF109907, AC005527, AC006547, AC000041, AC002091, Z46773, AJ003147, AC005209, AC002425, AL035089, AL031589, AC004895, AL035681, AL031053, Z82173, AC004408, AC006270, AC005212, AF111167, AC006132, AC003955, AL110292, AL031346, AC006285, AC006001, AL080243, AC005180, and AC005184.
HBJKD60	9446	740171	1 - 888	15 - 902	R77172.
HBJKD50	9447	724159	1 - 357	15 - 371	AA303007, AA630672, AA634147, N22465, AI249447, AA679532, AA478048, AI821670, AI357823, AA613249, AW274349, AI524360, AI254913, AI696962, N22023, AI590906, AW264934, AA012982, AA688359, AI791913, AW270258, AI792133, AW303196, AA169245, AA580808, AI821714, AA528554, AA631517, AL119552, AA188664, AW301350, AA631507, AA483771, AW304580, AA480574, AA112924, AL048135, H73863, AI580250, AW270270, AC006455, AL121754, AP000350, AC002425, AC004778, Z83844, AP000155, AF111168, AC002540, AF190465, AL109798, AC007312, AL121655, AC004859, AC006077, AC002369, AC004876, AC002126, AP000151, AP000009, AC007686, AP000501, AC002472, AP000690,

						AL109984, AL035587, AL078602, AL031733, AL009183, AL031311, AC006040, AC003663, AC007664, AC000353, AF165175, AC005632, U91323, AC006088, AP000113, AP000045, AC002303, AF165926, AF117829, AC005355, AC007314, AC005822, AC004790, AF109907, AC006121, AL078584, AF207550, AP000039, AF068006, AL121658, AC005534, AC006241, AF184110, AC005015, AL034421, AC002477, AC005102, AC004895, AC004851, AC007285, AC005666, AC005037, AC002400, AC005005, AL021918, AC006001, AL022238, AC002565, AL049539, AC007938, AF134726, AP000692, AC007536, AC006511, AC005620, AC007774, AL021154, U52112, AC006111, AL031659, AL022326, AF088219, AC006406, AL049712, AL033527, AL022323, AC005479, Z82244, Z92547, AL080243, AL049761, AL121653, AC003007, AF129756, AL078463, AL021977, AP000505, AC007793, AF036405, AB023048, AC005324, AC007785, AC006953, L44140, AC003108, AC005210, AC004098, AC007546, AL049766, AC005200, AC004834, AC007227, AL035249, AP000030, AP000493, AL031846, AF030876, AL117694, AC006459, AP000245, AC004139, AC005799, AL121603, AF029308, AC008072, AC005841, Z95114, AC004671, AC004985, AF141309, Z49235, AC002551, U95742, AC002994, AC007687, AC005013, U91326, AC004000, AL031056, AC005071, AC008115, AC005409, AC007242, AC004858, AC006059, AC004024, AC007022, AC007216, AC002316, AL049843, AC005993, AL035455, AB023054, AC007845, AL023807, AC005837, L78810, AC004821, AC007731, AC005229, AC004525, AC005500, AF001548, AL023575, AC007011, AP000010, AC005745, Z98051, AF030453, AL020997, AL132777, AC006167, AC006449, AC002553, AL035454, AC005154, Z93020, AC008044, AL031276, L78833, AL021978, AC005772, AC005599, AC006977, AC004263, AC005081, AP000555, AC005899, AC005274, AC005157, AF205588, AC002544, AL031230, Z81364, AL022336, AC002301, AC005088, AC004400, AL096774, AP000696, AL050321, AC007040, AL035415, Z83845, and Z84466.
HBJKD49	9448	847857	1 - 413	15 - 427		
HBJKD40	9449	710931	1 - 351	15 - 365		
HBJKA77	9450	771982	1 - 552	15 - 566	AA256446, AI806202, AA746104, and AA811237.	
HBJKA01	9451	916077	1 - 528	15 - 542	AI445151.	
HBJJX53	9452	835733	1 - 379	15 - 393	AA477047, AW383764, AA321993, AA309810, W25768, AA465618, R24995, W07130, R50327, AA368102, N58603, AA356448, AW015964, W69552, AI791923, AA525463, AA526678, AI792408, AC005071, AF161081, and AF161080.	
HBJJT12	9453	894345	1 - 604	15 - 618	AA113985, AA010096, AA333937, and U26150.	
HBJJN02	9454	919371	1 - 555	15 - 569	Z78294, AA808842, AA715173, AA715075, AC005102, AC006449, AC005697, AL031311, AC007277, AC004686, AC009247, AC006211, AL096701, AL080242, AC004125, AC005914, AF207550, AC004659, AC005746, AC004491, AC006947, AL023879, AC006487, AL020997, AC005940, AC004827, AC006115, AC016025, AC005189, AF196972, AF109907, and AC007057.	
HBJJL10	9455	937583	1 - 201	15 - 215	AA285172.	

HBJJE44	9456	716409	1 - 564	15 - 578	AI142126, R54554, H24334, AI142097, and AW374108.
HBJJA32	9457	699059	1 - 695	15 - 709	AI820773, H30102, H39985, H21775, AI668592, AI821454, R49787, H28487, and AC007200.
HBJJA01	9458	916078	1 - 1042	15 - 1056	AI088489, AA194062, AI123551, AA759303, AW028108, AI093432, AA836264, AA767044, AI274044, AI434773, AW135037, AI808043, AA806714, AW087576, AA883729, AA809688, AA847203, AI524547, AA865016, and AC004982.
HBJJL42	9459	597100	1 - 399	15 - 413	R35568.
HBJJL36	9460	861363	1 - 776	15 - 790	AI091292, AI005391, AA806165, AI002979, AI702990, AA158537, N54188, AA069178, AA091807, AA095638, and AC006146.
HBJJH60	9461	930448	1 - 517	15 - 531	AA729724, and AC006116.
HBJJF51	9462	725081	1 - 449	15 - 463	H69862.
HBJJF31	9463	697753	1 - 673	15 - 687	T79551, T86369, R98540, and T98454.
HBJJB69	9464	754891	1 - 531	15 - 545	H69017, and H69779.
HBJJA80	9465	784267	1 - 625	15 - 639	AA147107, AA425502, R79257, H03146, W58353, C19029, AA657402, AI050680, AA757308, AI963898, AA953652, AA369798, AI393329, U48339, T85056, and AA443785.
HBJHX73	9466	971377	1 - 1045	15 - 1059	AI148152, D51250, D80253, D80043, AW242597, D59787, D80219, D59275, D80227, D80240, D80210, D51423, D80134, D59619, D80193, D80391, AL039085, D80196, C14227, D80949, T23947, D59927, AL039538, AL039564, AL039156, AL043441, AL039150, AL038821, AL043445, AL039509, D80366, AL039108, T24119, AL039678, AL039074, AL038837, AL039625, AL039648, AL039629, D80168, T24112, AL037726, AL038531, AL039566, AL039109, AL040992, AL039924, AL039128, AL044407, AL039659, AL036973, AL039386, AL045337, AL037051, AL045353, AL036725, AL039423, AL045794, AL045341, AL039410, AL042909, AI535983, H00069, AL038025, AL044530, AL043422, T11051, D81026, AL043423, D80045, D50995, C14014, C75259, R47228, AL036418, AI535783, AW013814, AW452756, D59889, AW451070, C15076, AL037526, AL037639, D80022, D80195, AL036196, D80038, AL037615, AL038851, AL037082, T23659, D81030, D58283, T11417, T02921, D80188, D51799, D80378, D59467, AL036924, F13647, AL036117, AI557751, AL036767, T03269, AL036679, AL037601, AL036238, D80522, D80212, D50979, AL036190, AL036733, C14298, T48598, AL036964, Z21582, D59502, AA285331, C14429, D80164, AA514190, D59695, AL036158, D80166, AL037027, D59859, D80269, D80268, AL037054, AL037178, D52291, Z25782, D58253, AL036191, D80024, AL036765, AL036227, D57483, Z99396, D59610, C14389, D59627, D80241, D81111, AL036998, AI910186, AL037177, C14331, AL036207, D51060, H00072, AA305409, AL037021, AW178893, AL036174, D51079, AL037047, AW450376, AW177440, AL036139, D51022, AW179328, AL036167, D80014, AW178775, AA305578, AW378532, AL036132, D51213, AW352158, AW377671, AI905856, AW369651, D80251, D80064, D51097, AA514188, D80248, AW178762, AL037077, AW177501, AW177511, AL037002, AW360834, AI557774, AA514186, D80133, AW360811, T02974, D80302, AW352117, C05695, C14407, AW176467, AW375405, AW378540, Z25783, AW366296, D80132, AW360844, AW360817, AW375406,

					AW378534, AW179332, AW377672, AW179023, AW178905, D80247, AW179220, AL037679, D80258, D80439, AW377676, AW352171, AW178906, AW352170, AW177731, D59373, AW378539, AW178907, AW179019, AW179024, AL036858, C14077, AW177505, D80157, AW360841, AW179020, C06015, AW178909, AW177456, T03116, AW179329, AW178908, AW178980, AW135155, AW177733, AW378528, A25909, A67220, AR025207, X68127, A85396, A85477, A86792, D34614, U87250, A44171, AB012117, I18371, AR062871, AR037157, AR017907, AR062872, AR062873, AR067731, AR067732, A58522, A91750, A84772, A84776, A84773, A84775, A84774, A20702, A20700, A43189, A43188, AR066482, Y17188, AR008430, I68636, A02712, A95051, A95117, AR031374, A49700, AR031375, A58521, AR020969, X73004, A38214, I56772, I95540, AR018924, A63067, A51047, A63064, AR018923, A48774, A63072, A48775, AR068507, AR068506, AR015960, AR000007, AR015961, AR036905, AJ244003, AJ244004, AJ244005, I19516, A18053, I06859, A23334, A75888, I70384, A60111, A23633, A23998, A95052, A18050, AR007512, A98767, A93963, A93964, I63120, AR043602, AR043603, AR043601, I66494, I60241, I60242, A97211, Z96142, I00074, A58524, A58523, I92483, AR038286, I66495, AR054109, I66498, I66497, I66496, I66486, I66487, A64081, A24783, A24782, I03665, I03343, A81878, I03664, A15078, E00523, V00745, AF156296, AR036903, D28584, AR022240, A11245, A02710, E12615, AR035193, A92133, E14304, A07700, A13392, A13393, I19517, A27396, A76773, E13740, A22413, AR027100, I28266, I21869, I13349, A49045, E16678, A82653, E16636, A93016, AF118808, A70040, A35536, A35537, A02135, A02136, A04663, A04664, I01992, I25027, I26929, I44515, I26928, I26930, I26927, A58525, I08051, I25041, AF156294, Y11923, E16590, AJ230933, I19525, Y11926, D88984, AR038762, I49890, I44516, AR000006, I00077, A92636, D14548, A58526, A91753, I00079, A51384, E03165, E02221, E01614, E13364, S70644, D26022, AF019720, A91754, AR035975, AR035974, AR035977, AR035976, AR035978, X58217, A18722, I84554, I84553, A60957, M32676, S78798, AF096810, A60968, AF096793, A60985, A60990, A60987, A62300, AF156299, A62298, D44443, AB007195, X15418, A97221, A80951, A10363, X67155, I07429, X73003, I08250, E04616, AF130655, S65373, A84916, A10361, AJ132110, AF156303, S69292, AF156302, AF156304, A78862, D89785, A91965, I07888, I69350, A04710, A20701, Y11920, AR027069, A52326, X13220, AR018138, AR064706, D88547, I03663, S83538, Y11449, A02711, X92518, AR063812, A04447, and A04448.
HBJHW74	9467	765380	1 - 435	15 - 449	AA716676, H63334, H60316, AI744524, AA836358, Z95116, AC005529, U91321, AC004832, AL034429, AL049874, AC005796, AC005527, AL049539, AL109758, and AL132777.
HBJHU20	9468	907575	1 - 544	15 - 558	AA179630, and AA176615.
HBJHO44	9469	882040	1 - 409	15 - 423	R96772.
HBJHI96	9470	828996	1 - 424	15 - 438	AA461038, AW151827, AI753072, AI042290, AI377120, AI364168, W68727, N30339, AI754813, AI203980, AA921913, AI754315, AW162458, AI076713, AI281214, AI457783, AW080473, AW338260, AW291880, AW337350, AI913188, AI243887, AA291380, H73392, AA702481,

HBJHG02	9471	919450	1 - 643	15 - 657	AA126455, and AA805265.	AI095058, AI439501, AW026886, AI831262, AI961995, T54990, AA578659, AW058379, AI921073, H58220, AA055896, T56868, AW073087, AA403311, R94192, AA410982, AI566606, T54669, AI814941, AA680075, AA852300, AA131298, AI686560, AA600068, AI380408, AI694164, AA338172, AA853557, AA304609, AA332521, R94291, AA131543, AW198197, W68749, N56676, AA377810, H58556, AA055184, W58726, AA570322, AA347235, R75738, AA419374, W51998, W52829, AI280595, AA366339, AI537499, AA347234, and AA253337.
HBJGT03	9472	923800	1 - 497	15 - 511	AW014944, AI571386, AI494432, AW149677, and AC007682.	
HBJFR45	9473	722105	1 - 519	15 - 533	AW205972, and R06326.	
HBJFQ08	9474	959190	1 - 326	15 - 340		
HBJFP52	9475	728580	1 - 471	15 - 485	R33062, and R26486.	
HBJFP08	9476	959868	1 - 474	15 - 488	AA463369.	
HBJFK85	9477	783432	1 - 292	15 - 306	AL036438, and R43453.	
HBJFI48	9478	847899	1 - 489	15 - 503	AC005180.	
HBJFI30	9479	691056	1 - 440	15 - 454	H83540, H83349, T98751, and T89066.	
HBJFH60	9480	740543	1 - 552	15 - 566	AI631029, N51923, H64804, AW016151, N51665, N53749, AA503053, AA917715, R81860, and N50398.	
HBJFH06	9481	935587	1 - 675	15 - 689	AA189094.	
HBJFD41	9482	711591	1 - 638	15 - 652	AA120846, N94144, and AA120845.	
HBJFD21	9483	671205	1 - 869	15 - 883	W89209, AA236825, T90638, AA255865, AW137746, AA814395, AA814416, AA825532, T83165, and T82244.	
HBJFC23	9484	423885	1 - 616	15 - 630	AW276648, R21362, H10771, AW376712, AI907952, AW407979, AW366716, H08663, and AB028960.	
HBJFB10	9485	968162	1 - 421	15 - 435	AI040621, H71636, T80789, and AL035086.	
HBJEY89	9486	787044	1 - 309	15 - 323	W59951.	
HBJES09	9487	487020	1 - 547	15 - 561		
HBJEP70	9488	757374	1 - 476	15 - 490	R64066, and R64081.	
HBJEN68	9489	752251	1 - 594	15 - 608	H48332, H53781, and H48241.	
HBJEM45	9490	722107	1 - 306	15 - 320	N35747.	
HBJEL04	9491	615515	1 - 480	15 - 494	H90849, H78133, and AI023482.	
HBJEJ06	9492	935967	1 - 385	15 - 399	H37882.	
HBJEE72	9493	766187	1 - 516	15 - 530	AI739168, AI243692, R61551, AI423731, R53934, AA426249, T06305, AI423751, AA805323, and AA736849.	
HBJED51	9494	485130	1 - 485	15 - 499		
HBJED05	9495	935058	1 - 459	15 - 473	T19837, Z42292, W56491, Z43884, R10274, H61521, AA047587, AI557059, AA001460, R21700, R56331, H58106, W68068, AI879218, AI902942, AW391832, H71164, F06897, and Z28851.	

HBJEC67	9496	573809	1 - 424	15 - 438		
HBJEA73	9497	573834	1 - 105	15 - 119		
HBJEA54	9498	625943	1 - 507	15 - 521		
HBJEA38	9499	577103	1 - 598	15 - 612	W85789, AA693974, AI032087, and W85723.	
HBJEA37	9500	839964	1 - 96	15 - 110		
HBJEA13	9501	419107	1 - 255	15 - 269		
HBJDZ49	9502	847928	1 - 383	15 - 397	AI018729, AI017735, T94096, AA788760, AC004878, AC006014, AC005488, AC005071, AC006480, AF030453, and AC005088.	
HBJDR24	9503	677407	1 - 415	15 - 429	R96956.	
HBJDQ86	9504	784654	1 - 422	15 - 436	N92225.	
HBJDM70	9505	757435	1 - 386	15 - 400	H02200.	
HBJDL24	9506	678272	1 - 624	15 - 638	R92654, R92648, and N59587.	
HBJCV85	9507	900955	1 - 807	15 - 821	D58283, D80195, D80227, D80391, D80166, D59859, D80043, D59502, D51423, D59619, D80210, D51799, D80240, D80253, D80196, D80269, D80038, D80188, D80212, D59275, D80193, D57483, D59927, D80219, D81030, D80022, D50979, D59889, D59610, D80366, D80378, D80045, D59787, C14429, D50995, D80164, D81026, D80241, D80024, T03269, C15076, C14389, C75259, C14014, C14331, D59467, D51060, AW178893, AA305409, D80134, F13647, D51250, D80268, D58253, D80949, AA305578, D80168, C14227, D51079, D81111, D51022, AW177440, AW179328, D80522, D52291, AW178775, AW378532, D59695, AW352158, AW377671, Z21582, AI910186, AW369651, AI905856, D80251, AA514188, D80248, AW178762, AA514186, D51097, AA285331, C05695, C14298, AW177501, AW177511, D80064, D80133, AW360811, C14407, AW352117, AW176467, AW378540, AW375405, AW360834, D80132, AW366296, AW360844, AW360817, AW375406, AW378534, AW179332, AW377672, AW179023, AW178905, AW179220, D80302, AI557751, AW352171, D80439, AW377676, AW178906, AW352170, AW177731, AW178907, AW179019, AW179024, D59373, D80247, D80014, AW177505, AW179020, AW360841, AW178909, AW177456, AW179329, AW178980, AW177733, AW378528, AW178908, AW178754, AW179018, AW352174, T11417, D51103, T03116, AW179004, AW179012, AW178914, AW378525, D80157, AW367967, AW177722, AW177728, T02974, D51759, AW179009, AW178774, AW178911, AW378543, AW352163, D58246, C06015, D59503, D80258, AW178983, AW352120, AW178781, T48593, D51213, AW378539, D59627, AI557774, D58101, AI535850, AA809122, AW177723, D59653, AW177508, D45260, C14975, AI525923, AW378533, AW367950, H67866, D59317, H67854, C03092, D45273, AW177497, AI535686, AW178986, N66429, AW177734, AI525917, C14973, C14344, D59474, AI525227, D51221, D59551, D60010, AA033512, AI525920, AA514184, D60214, C14957, C14046, C16955, T03048, AI525242, AI525235, AI525912, AI525925, AI535961, AW378542, AI525215, C05763, Z33452, AI525237, AI525222, D31458, AJ132110, A62300, A84916, A62298, X67155, A67220, D89785, A78862, D26022, A25909, Y17188,

						AR018138, D34614, D88547, AR025207, X82626, AB028859, AF058696, AR008278, I82448, X68127, AB012117, Y12724, A85396, AR066482, A44171, A85477, I19525, A86792, U87250, X93549, A82595, AR060385, A94995, AB002449, AR016808, AR008443, I50126, I50132, I50128, I50133, AF135125, AR066488, AR016514, AR060138, A45456, A26615, AR052274, Y09669, A43192, A43190, AR038669, AR066490, AR066487, I14842, A30438, I18367, D88507, AR054175, D50010, Y17187, AR064240, AB033111, A63261, AR008277, AR008281, AR008408, AR062872, A70867, AR016691, AR016690, U46128, I79511, D13509, A64136, A68321, AR060133, U87247, Z32749, AB023656, U79457, AF123263, Z82022, AR032065, AR060382, X93535, and AR008382.
HBJCQ65	9508	876430	1 - 1780	15 - 1794		AI828112, AI762456, AI669527, AW270041, AW005454, AI742020, AI813489, AW055057, AW438593, AA702328, AI379307, AA262137, AA643040, AA694381, AA281632, AW243902, AI422791, AA493261, AW117912, AI034474, AW236597, AW440103, AI292303, AA281692, D19612, AA768827, N99706, AI081788, AI868989, AA514538, AA877024, N71978, R24110, AW449526, R17044, AW082476, AA369546, R24059, AI290151, R26499, AI383270, AA612940, AW082653, R50985, C16425, R26471, AI701667, D62032, AA262413, AA333518, AW082649, AA722211, AI539327, AA369545, AW021723, R17005, AA468881, AA522467, AI371310, N93082, and W24736.
HBJCJ82	9509	779645	1 - 467	15 - 481		
HBJCE07	9510	954090	1 - 180	15 - 194		R02678.
HBJCB83	9511	781411	1 - 617	15 - 631		T88832.
HBJBR04	9512	847952	1 - 432	15 - 446		AW206286, AW291675, AW025778, T99524, AW026757, and AC005682.
HBJAP95	9513	796659	1 - 263	15 - 277		N89814, AA209448, AW239298, AP000541, and AJ239321.
HBJAO55	9514	732436	1 - 414	15 - 428		T81741, AA778192, W85729, and AL132777.
HBJAJ49	9515	723164	1 - 427	15 - 441		N71474.
HBJAI50	9516	724619	1 - 490	15 - 504		AI089358, AA056686, AI089564, AI086521, AI669927, AI817821, AA056582, AA847148, AI827763, and AB002370.
HBJAH27	9517	682941	1 - 239	15 - 253		
HBJAE32	9518	699695	1 - 395	15 - 409		W88646, AI368895, and Z39215.
HBJAB77	9519	772422	1 - 491	15 - 505		H53026.
HBJAB49	9520	722195	1 - 874	15 - 888		AI479236, AI935423, AA255972, and AA243356.
HBJAB28	9521	847966	1 - 486	15 - 500		Z28561.
HBJAB15	9522	660552	1 - 395	15 - 409		AA429379.
HBDAE47	9523	720008	1 - 572	15 - 586		AA252703, AI760942, and AA565583.
HBDAD64	9524	864344	1 - 534	15 - 548		H04563, R80434, AA531428, Z82215, and Z95114.
HBDAD16	9525	661560	1 - 375	15 - 389		AI810593, and T89570.
HBCCO10	9526	963157	1 - 564	15 - 578		AA701314, and AA004793.

HBCCJ05	9527	930956	1 - 568	15 - 582	H59931, H67432, Z70280, AC003100, AC006998, AC003072, AC005154, AL022154, and AC003034.
HBCCE11	9528	965869	1 - 579	15 - 593	AI672457, AA810483, AI269914, AI949892, AI198001, W86511, AW237699, AI863804, and AI525426.
HBCCD06	9529	938319	1 - 590	15 - 604	AI078128, AI871101, AI274339, AA035467, AA419038, AI479404, AI677732, AW190726, AI198435, AA031617, AI283200, AI983969, AA411122, AI093316, AI361637, AI769275, AI560217, AA961077, AI291805, AI291474, AA915909, AA035466, AA046943, AI857306, AA661657, AA427407, AA725194, AA423792, AW070742, AW051192, AI275083, AW293787, AW452102, AA250784, AA031475, N92812, H91759, AW149476, H91665, and AA514348.
HBCCB51	9530	975256	1 - 515	15 - 529	
HBCBR08	9531	958151	1 - 567	15 - 581	AA280776, AL137689, AF111173, and AF100172.
HBCBN51	9532	952057	1 - 995	15 - 1009	AA464030, AA434281, AA410674, D78694, AI860751, AI628190, AA568168, AI097605, AI199027, D78920, AA227411, AI200649, AI199599, AI935345, AA525327, AI475176, AI910441, AI923458, AI247190, AI687257, AI923451, AI541551, AI699991, AI653151, and AW438934.
HBCBN06	9533	934110	1 - 525	15 - 539	H40594.
HBCBG04	9534	926761	1 - 588	15 - 602	AA677024, and AI022041.
HBCBF12	9535	969578	1 - 517	15 - 531	AI566483, AA417101, and AL021368.
HBCBE57	9536	848322	1 - 758	15 - 772	AA486018, AA005417, H56995, AL031666, and AF144233.
HBCBB22	9537	848325	1 - 895	15 - 909	AA419501, AA969163, AA157911, AA410996, AW452982, AW339854, and H14554.
HBCAW52	9538	573919	1 - 349	15 - 363	AA826669, AA287363, AI809776, AA470582, AA516190, AA505108, AA838091, AI680323, AA947361, Z97054, AL049694, AC005484, AC004253, AC005288, AC004019, AL049757, AC004584, AC006441, AC009247, AC007395, AC004216, AC004895, AL022316, U91318, U95742, AL049766, AL009181, AL023553, AC016830, AC002350, AC007216, AC000052, Z85986, AC007676, AC005562, AC016027, AC005822, AL031848, AL050318, AL031662, AC006088, AC003950, AC005086, AC004099, AB001523, AP000694, AC004841, AC010205, AC004765, AC005280, AC004813, AL109984, AC005409, AC003101, AC004678, AC004812, AP000514, AL034429, AC004874, AL031602, AC006487, AJ009610, AC004596, AL136295, AC002314, AC007227, AL117694, AP001060, AC004125, AL031587, AL133246, AC005057, AF001548, AP000512, AC005004, AC005088, Z83844, AL031311, U91323, AC007686, AF001549, AL022165, AF030453, Z98941, Z84469, AC004383, AC005914, Z93016, AC005516, AL049569, AC006059, Z93017, Z83847, AC005837, AC004913, AF217403, AC005015, AC004662, AC005081, AC007193, AC008039, AC003982, AC005058, AC006130, M89651, AC008372, AF043945, AC005696, AL096701, AL024474, AC002312, AL031276, AC004531, AL009183, AL049776, AL049780, AC005821, AC003046, AF134726, AL096712, AL031985, AL049758, AL035249, AL023807, AP000501, Z93241, AL133382, AC005940, AC010077, AC008101, AL035086, AC006430, AC002425, Z86090, AC005082, AC007899, AC005049,

						AL024507, AC006064, AF207550, AL135960, AJ131016, AC006312, AC006254, AC004477, AB023049, AC005037, AC002563, AF165926, AC007199, AC004551, AL022302, AL049795, AC007191, AC005920, AC002115, AC004650, AC004694, D84394, AC005046, AL031133, AC005808, AL035659, AC009516, Z84480, AC007666, AC005529, AL049830, AC005668, AL031229, AC008040, AC006211, AL008723, AF053356, Z82244, AL022476, AL049759, AL133163, AL031283, AL109758, AP000032, AP000103, AC004851, L78810, AL080317, AP000134, AP000212, AC004817, AC002316, AL021939, AC006141, AP000689, AC006539, and AL035458.
HBCAT10	9539	968195	1 - 323	15 - 337		AI351598, and AL021528.
HBCAS32	9540	699489	1 - 264	15 - 278		H39875.
HBCAQ85	9541	783431	1 - 362	15 - 376		R60453, H10942, and Z42911.
HBCAQ42	9542	864356	1 - 418	15 - 432		AA594734, AA376358, N69399, AI623364, AA368329, AI733856, AI246386, AA077619, AA133013, AI246061, AA878492, AI689198, AA299422, AI268019, T53133, AI273990, AA484022, AA211918, H73550, AW161459, AA434078, W26972, AA831638, AA614647, AW161879, M78026, AI191343, AI811846, AI003797, AA814878, AA936548, AW268329, AA714524, AA804334, H67064, AW069227, F33126, AA504951, T08386, AI905588, AI491765, H24953, AI634187, AA584207, AI457313, AI280574, AA356376, AI243793, AA363027, AA344645, AW007980, AA706202, AA226357, AW378516, AA325115, AI744933, C14966, AA226356, AI049630, F32591, AA568399, AA058312, AI052776, AA809089, AI904840, AA598605, H65213, AA568400, AA568416, AW378511, AW270429, AA565319, AA425924, AI926717, AW270351, AI821420, AI697425, T47138, AA862312, AL042735, AA573693, AI805261, AI054090, AA514450, AI469392, AI368862, AA357878, AA525331, AI718462, AI568147, C15504, AI332615, AA363003, AA523695, AW068786, AA714512, H44944, AA526216, AI683116, AW243793, AL033392, AC004491, AC005231, AL022326, U62293, U63721, AC005057, AP000516, AC002375, AL031280, U02051, AC005944, AC004801, AC007666, AL031602, AL022311, AP000696, AL022324, AP000690, AC005585, AC004662, AJ251973, AL078638, AC007308, AL031595, AC002470, AC003030, AC005280, AC002492, AL049646, AC006050, Z93244, AL031665, AL020993, AL049563, AL031291, AP000501, AL109627, AC005015, AC005786, AF165926, AC006600, AF031078, AC005412, AL133243, AL031289, AC007376, AC005317, AF030876, AC004703, AC004382, AL035455, AP000689, AC005829, AL031007, X58139, AC009510, AC007686, U47924, AC006011, AC005011, AL022320, AC004973, AC004865, Z94802, AC005670, AL135959, AC007707, AC007685, AC002558, AB013139, AL031431, AB020690, AC006120, AC007358, AB000931, AC005393, AC005908, AC000025, AC004651, AC005316, AC004760, AC003071, AC005031, AL031577, AC000052, AC004817, AC005837, AL022721, AC007880, AC002115, U63834, Z82250, AF043460, AC007390, AL078602, AC007263, U78027, AC004230, M84472, AL079342, AL035682, AC005214, AL022334, AC004796, AC007444, AF051976, AC000125, U91326,

						AC005913, AP000692, AC004912, AC005747, AL035422, Z95116, AL035461, AC007543, Z84469, AP000172, Z93017, AF069291, AL035685, AC004910, AC000039, AP000057, AC006254, AC004966, AC004890, AC005215, AC003956, AP000552, AP000125, AC005277, AC006211, AC004217, AL022332, Z98044, Z83846, AC005480, AC003037, Z94161, AP000701, AP000272, AC005207, AL096791, AP000695, U34879, AC004832, Z84487, AC005216, AC003004, AF008191, AF049895, AC006130, AC002395, AL109839, AC003963, AL035420, AL022726, AF035453, AC006561, L78810, AL078634, AC002425, AF035968, AC006581, U91318, AC005233, AL031387, AC004849, AC006552, Z85997, AD000092, AC005539, AL121653, AL049872, AD000813, AC004834, Z97630, Z81010, AC007406, AC004922, AC002477, AC006251, AL023876, AC006596, U51561, AC007160, AC005049, Z82244, AP000210, AP000132, AC002091, AL035681, AL109865, AC005924, AC005225, AC004891, AC004752, AC003029, AF002993, AL031257, AC007421, AC004636, AC007899, AL035690, AC006160, Z99127, AC006141, AL009051, AP000556, AF001548, AC004638, AC005048, AC007773, AC005335, AL049743, AC004263, Z93023, AC004997, U85195, AC005632, AC004988, AC009946, AL096701, AC009516, AC005082, AL049699, AC004151, AC006443, AC007842, AL049745, AC005089, AC003077, AP000114, AP000046, AC005383, and AC002044.
HASCG58	9543	738423	1 - 489	15 - 503		T83649, AW450374, AI079410, T92067, AA031273, F24833, AI129738, AA031274, R10134, R24168, and AA625541.
HASAW90	9544	789112	1 - 822	15 - 836		N42137, AA416659, AI587031, R18649, AA416660, D78802, AW182288, and N33742.
HASAR74	9545	879377	1 - 1185	15 - 1199		AW302315, AA644090, AI962030, AA601356, AI040051, AI345721, AA483606, AL040054, AA568204, AA570740, AA584489, AW188742, AA581263, AA714011, AA749235, AI061313, AA687730, AA503298, AA838190, AI251576, AW021917, AA862243, AA640305, AA626040, AI499954, AA347114, AL135357, AA584482, AI207424, AI583466, AA121777, AA182731, D87008, D88268, AC007382, AL031177, AL008719, AL079304, AC005274, AC004615, Z96074, AC008082, AC005406, AL023283, U95743, AL117329, AC005071, AL035405, AC004866, AC002449, AL136297, AC004097, AC005010, AC005744, Z98304, AL049839, AC005829, AC000403, AC004672, AC005231, AL020997, AC000038, M89651, AC006454, AC005280, Z85996, AL035697, AC012627, U85195, AC006581, AE000658, AC004883, Z97054, AC006487, AL049636, AL023553, AC005184, AC004020, AL034421, AL031584, AC009516, AC010206, AL022323, U95741, AC002984, AL121694, AC007981, AP000208, AP000557, AC005013, AC002542, Z82201, AC005821, AC005899, AL117352, AL031466, AC005512, AC005261, AC004804, AP000247, Z95114, AL031767, AP000130, AC006101, AC006459, AC003071, U96629, AL049631, Z83822, AC006162, AC005786, AC004913, AP000030, AC005562, AC004706, AC005049, AC010582, AL031289, AL021397, AC006001, AC006285, AC005411, AC005778, AC005874, AF134471, AP000501, AC004814, AL080241, AC004837, AC007546, AL109628, Z84480, AC007052, AC006445, AL109798, AP000212, AP000134, Z98946,

					AC009396, AL021155, AF172277, AC004687, AC002310, AC007461, AC000378, AL079342, AC003004, AL008718, AL022316, AF217403, AL031311, AC005224, AC004222, AL031650, AP000086, AL078639, AC007664, Z69710, AP000251, AB000877, AC004975, AC007792, AL135783, AC004491, AC007406, AC005529, AC007055, AL035587, Z82203, AC002504, AC004707, AC002350, AC005940, AL050333, Z93023, AL135744, AP000516, AC007919, AC004859, U78027, AL035684, Z81364, Z84466, Z95115, Z85987, AC004128, AC006046, AC004386, AC005884, AC004775, AL035422, AC005544, AC007541, AL031733, AC005088, AL035420, Z85986, AC002091, AC009247, AC005519, AC005907, AC002558, AL139054, AC000385, AL136295, AC007488, AP000506, AC006211, AC007225, AC000025, AC005527, AL031431, AC005412, AC004797, AC005587, AC002369, AC004865, AC005683, AP000502, AL050338, AF134726, AC008132, AL136504, Z75887, AC005578, AL137191, AL030995, AF109907, AC006088, AB000882, AC002375, AL008627, AC005042, AC004659, AL021807, AF099810, AC004125, AC005377, AC007676, AF024534, AD001527, AC002119, AC004841, AC006333, AL109952, AC005921, AL035072, AC004694, AP000065, AC005015, AL050308, Z98200, AC006530, AC004156, AC002486, AC004453, AL078581, AC011311, AC005919, AC002416, AC004598, AC006241, and AF001549.
HASAC10	9546	968746	1 - 470	15 - 484	AI863136, N71484, AA318470, AA972121, AW129333, and AC007677.

TABLE 4

Code	Description	Tissue	Organ	Cell Line	Disease	Vector
AR022	a_Heart	a_Heart				
AR023	a_Liver	a_Liver				
AR024	a_mammary gland	a_mammary gland				
AR025	a_Prostate	a_Prostate				
AR026	a_small intestine	a_small intestine				
AR027	a_Stomach	a_Stomach				
AR028	Blood B cells	Blood B cells				
AR029	Blood B cells activated	Blood B cells activated				
AR030	Blood B cells resting	Blood B cells resting				
AR031	Blood T cells activated	Blood T cells activated				
AR032	Blood T cells resting	Blood T cells resting				
AR033	brain	brain				
AR034	breast	breast				
AR035	breast cancer	breast cancer				
AR036	Cell Line CAOV3	Cell Line CAOV3				
AR037	cell line PA-1	cell line PA-1				
AR038	cell line transformed	cell line transformed				
AR039	colon	colon				
AR040	colon (9808co65R)	colon (9808co65R)				
AR041	colon (9809co15)	colon (9809co15)				
AR042	colon cancer	colon cancer				
AR043	colon cancer (9808co64R)	colon cancer (9808co64R)				
AR044	colon cancer 9809co14	colon cancer 9809co14				
AR045	corn clone 5	corn clone 5				
AR046	corn clone 6	corn clone 6				
AR047	corn clone2	corn clone2				
AR048	corn clone3	corn clone3				
AR049	Corn Clone4	Corn Clone4				
AR050	Donor II B Cells 24hrs	Donor II B Cells 24hrs				
AR051	Donor II B Cells 72hrs	Donor II B Cells 72hrs				
AR052	Donor II B-Cells 24 hrs.	Donor II B-Cells 24 hrs.				
AR053	Donor II B-Cells 72hrs	Donor II B-Cells 72hrs				
AR054	Donor II Resting B Cells	Donor II Resting B Cells				
AR055	Heart	Heart				
AR056	Human Lung (clonetech)	Human Lung (clonetech)				
AR057	Human Mammary (clontech)	Human Mammary (clontech)				
AR058	Human Thymus (clonetech)	Human Thymus (clonetech)				
AR059	Jurkat (unstimulated)	Jurkat (unstimulated)				
AR060	Kidney	Kidney				
AR061	Liver	Liver				
AR062	Liver (Clontech)	Liver (Clontech)				
AR063	Lymphocytes chronic lymphocytic leukaemia	Lymphocytes chronic lymphocytic leukaemia				

AR064	Lymphocytes diffuse large B cell lymphoma	Lymphocytes diffuse large B cell lymphoma				
AR065	Lymphocytes follicular lymphoma	Lymphocytes follicular lymphoma				
AR066	normal breast	normal breast				
AR067	Normal Ovarian (4004901)	Normal Ovarian (4004901)				
AR068	Normal Ovary 9508G045	Normal Ovary 9508G045				
AR069	Normal Ovary 9701G208	Normal Ovary 9701G208				
AR070	Normal Ovary 9806G005	Normal Ovary 9806G005				
AR071	Ovarian Cancer	Ovarian Cancer				
AR072	Ovarian Cancer (9702G001)	Ovarian Cancer (9702G001)				
AR073	Ovarian Cancer (9707G029)	Ovarian Cancer (9707G029)				
AR074	Ovarian Cancer (9804G011)	Ovarian Cancer (9804G011)				
AR075	Ovarian Cancer (9806G019)	Ovarian Cancer (9806G019)				
AR076	Ovarian Cancer (9807G017)	Ovarian Cancer (9807G017)				
AR077	Ovarian Cancer (9809G001)	Ovarian Cancer (9809G001)				
AR078	ovarian cancer 15799	ovarian cancer 15799				
AR079	Ovarian Cancer 17717AID	Ovarian Cancer 17717AID				
AR080	Ovarian Cancer 4004664B1	Ovarian Cancer 4004664B1				
AR081	Ovarian Cancer 4005315A1	Ovarian Cancer 4005315A1				
AR082	ovarian cancer 94127303	ovarian cancer 94127303				
AR083	Ovarian Cancer 96069304	Ovarian Cancer 96069304				
AR084	Ovarian Cancer 9707G029	Ovarian Cancer 9707G029				
AR085	Ovarian Cancer 9807G045	Ovarian Cancer 9807G045				
AR086	ovarian cancer 9809G001	ovarian cancer 9809G001				
AR087	Ovarian Cancer 9905C032RC	Ovarian Cancer 9905C032RC				
AR088	Ovarian cancer 9907 C00 3rd	Ovarian cancer 9907 C00 3rd				
AR089	Prostate	Prostate				
AR090	Prostate (clonetech)	Prostate (clonetech)				
AR091	prostate cancer	prostate cancer				
AR092	prostate cancer #15176	prostate cancer #15176				
AR093	prostate cancer #15509	prostate cancer #15509				
AR094	prostate cancer #15673	prostate cancer #15673				
AR095	Small Intestine (Clontech)	Small Intestine (Clontech)				
AR096	Spleen	Spleen				
AR097	Thymus T cells activated	Thymus T cells				

		activated				
AR098	Thymus T cells resting	Thymus T cells resting				
AR099	Tonsil	Tonsil				
AR100	Tonsil geminal center centroblast	Tonsil geminal center centroblast				
AR101	Tonsil germinal center B cell	Tonsil germinal center B cell				
AR102	Tonsil lymph node	Tonsil lymph node				
AR103	Tonsil memory B cell	Tonsil memory B cell				
AR104	Whole Brain	Whole Brain				
AR105	Xenograft ES-2	Xenograft ES-2				
AR106	Xenograft SW626	Xenograft SW626				
H0004	Human Adult Spleen	Human Adult Spleen	Spleen			Uni-ZAP XR
H0013	Human 8 Week Whole Embryo	Human 8 Week Old Embryo	Embryo			Uni-ZAP XR
H0022	Jurkat Cells	Jurkat T-Cell Line				Lambda ZAP II
H0025	Human Adult Lymph Node	Human Adult Lymph Node	Lymph Node			Lambda ZAP II
H0031	Human Placenta	Human Placenta	Placenta			Uni-ZAP XR
H0050	Human Fetal Heart	Human Fetal Heart	Heart			Uni-ZAP XR
H0057	Human Fetal Spleen					Uni-ZAP XR
H0058	Human Thymus Tumor	Human Thymus Tumor	Thymus		disease	Lambda ZAP II
H0059	Human Uterine Cancer	Human Uterine Cancer	Uterus		disease	Lambda ZAP II
H0060	Human Macrophage	Human Macrophage	Blood	Cell Line		pBluescript
H0061	Human Macrophage	Human Macrophage	Blood	Cell Line		pBluescript
H0062	Human Thymus	Human Thymus	Thymus			Uni-ZAP XR
H0063	Human Thymus	Human Thymus	Thymus			Uni-ZAP XR
H0069	Human Activated T-Cells	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0073	Human Leiomyeloid Carcinoma	Human Leiomyeloid Carcinoma	Muscle		disease	Uni-ZAP XR
H0074	Human Platelets	Human Platelets	Blood	Cell Line		Uni-ZAP XR
H0075	Human Activated T-Cells (II)	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0083	HUMAN JURKAT MEMBRANE BOUND POLYSOMES	Jurkat Cells				Uni-ZAP XR
H0087	Human Thymus	Human Thymus				pBluescript
H0090	Human T-Cell Lymphoma	T-Cell Lymphoma	T-Cell		disease	Uni-ZAP XR
H0108	Human Adult Lymph Node, subtracted	Human Adult Lymph Node	Lymph Node			Uni-ZAP XR
H0109	Human Macrophage, subtracted	Macrophage	Blood	Cell Line		pBluescript
H0116	Human Thymus Tumor, subtracted	Human Thymus Tumor	Thymus			pBluescript
H0128	Jurkat cells, thiouridine activated	Jurkat Cells				Uni-ZAP XR
H0129	Jurkat cells, thiouridine activated, fract II	Jurkat Cells				Uni-ZAP XR

H0134	Raji Cells, cyclohexamide treated	Cyclohexamide Treated Cem, Jurkat, Raji, and Supt	Blood	Cell Line		Uni-ZAP XR
H0139	Activated T-Cells, 4 hrs.	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0140	Activated T-Cells, 8 hrs.	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0141	Activated T-Cells, 12 hrs.	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0158	Activated T-Cells, 4 hrs., ligation 2	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0159	Activated T-Cells, 8 hrs., ligation 2	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0160	Activated T-Cells, 12 hrs., ligation 2	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0161	Activated T-Cells, 24 hrs., ligation 2	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0167	Activated T-Cells, 24 hrs.	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0179	Human Neutrophil	Human Neutrophil	Blood	Cell Line		Uni-ZAP XR
H0185	Activated T-Cell labeled with 4-thioluri	T-Cells	Blood	Cell Line		Lambda ZAP II
H0186	Activated T-Cell	T-Cells	Blood	Cell Line		Lambda ZAP II
H0187	Resting T-Cell	T-Cells	Blood	Cell Line		Lambda ZAP II
H0189	Human Resting Macrophage	Human Macrophage/Monocytes	Blood	Cell Line		Uni-ZAP XR
H0191	Human Activated Macrophage (LPS), thiour	Human Macrophage/Monocytes	Blood	Cell Line		Uni-ZAP XR
H0202	Jurkat Cells, cyclohexamide treated, subtraction	Cyclohexamide Treated Cem, Jurkat, Raji, and Supt	Blood	Cell Line		Uni-ZAP XR
H0203	Jurkat Cells, cyclohexamide treated, dif	Cyclohexamide Treated Cem, Jurkat, Raji, and Supt	Blood	Cell Line		Uni-ZAP XR
H0218	Activated T-Cells, 0hrs, subtracted	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0219	Activated T-Cells, 0hrs, differentially expressed	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0220	Activated T-Cells, 4 hrs, subtracted	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0221	Activated T-Cells, 4 hrs, differentially expressed	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0222	Activated T-Cells, 8 hrs, subtracted	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0223	Activated T-Cells, 8 hrs, differentially expressed	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0224	Activated T-Cells, 12 hrs, subtracted	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0225	Activated T-Cells, 12hrs, differentially expressed	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0250	Human Activated Monocytes	Human Monocytes				Uni-ZAP XR
H0253	Human adult testis, large inserts	Human Adult Testis	Testis			Uni-ZAP XR
H0254	Breast Lymph node cDNA library	Breast Lymph Node	Lymph Node			Uni-ZAP XR
H0255	breast lymph node CDNA	Breast Lymph Node	Lymph Node			Lambda

	library					ZAP II
H0261	H. cerebellum, Enzyme subtracted	Human Cerebellum	Brain			Uni-ZAP XR
H0264	human tonsils	Human Tonsil	Tonsil			Uni-ZAP XR
H0265	Activated T-Cell (12hs)/Thiouridine labelledEco	T-Cells	Blood	Cell Line		Uni-ZAP XR
H0271	Human Neutrophil, Activated	Human Neutrophil - Activated	Blood	Cell Line		Uni-ZAP XR
H0272	HUMAN TONSILS, FRACTION 2	Human Tonsil	Tonsil			Uni-ZAP XR
H0274	Human Adult Spleen, fractionII	Human Adult Spleen	Spleen			Uni-ZAP XR
H0300	CD34 positive cells (Cord Blood)	CD34 Positive Cells	Cord Blood			ZAP Express
H0305	CD34 positive cells (Cord Blood)	CD34 Positive Cells	Cord Blood			ZAP Express
H0306	CD34 depleted Buffy Coat (Cord Blood)	CD34 Depleted Buffy Coat (Cord Blood)	Cord Blood			ZAP Express
H0318	HUMAN B CELL LYMPHOMA	Human B Cell Lymphoma	Lymph Node		disease	Uni-ZAP XR
H0341	Bone Marrow Cell Line (RS4;11)	Bone Marrow Cell Line RS4;11	Bone Marrow	Cell Line		Uni-ZAP XR
H0354	Human Leukocytes	Human Leukocytes	Blood	Cell Line		pCMVSport 1
H0369	H. Atrophic Endometrium	Atrophic Endometrium and myometrium				Uni-ZAP XR
H0370	H. Lymph node breast Cancer	Lymph node with Met. Breast Cancer			disease	Uni-ZAP XR
H0376	Human Spleen	Human Adult Spleen	Spleen			pCMVSport 1
H0393	Fetal Liver, subtraction II	Human Fetal Liver	Liver			pBluescript
H0402	CD34 depleted Buffy Coat (Cord Blood), re-excision	CD34 Depleted Buffy Coat (Cord Blood)	Cord Blood			ZAP Express
H0416	Human Neutrophils, Activated, re-excision	Human Neutrophil - Activated	Blood	Cell Line		pBluescript
H0421	Human Bone Marrow, re-excision	Bone Marrow				pBluescript
H0422	T-Cell PHA 16 hrs	T-Cells	Blood	Cell Line		pSport1
H0423	T-Cell PHA 24 hrs	T-Cells	Blood	Cell Line		pSport1
H0436	Resting T-Cell Library,II	T-Cells	Blood	Cell Line		pSport1
H0439	Human Eosinophils	Eosinophils				pBluescript
H0444	Spleen metastic melanoma	Spleen, Metastic malignant melanoma	Spleen		disease	pSport1
H0445	Spleen, Chronic lymphocytic leukemia	Human Spleen, CLL	Spleen		disease	pSport1
H0457	Human Eosinophils	Human Eosinophils				pSport1
H0477	Human Tonsil, Lib 3	Human Tonsil	Tonsil			pSport1
H0478	Salivary Gland, Lib 2	Human Salivary Gland	Salivary gland			pSport1
H0485	Hodgkin"s Lymphoma I	Hodgkin"s Lymphoma I			disease	pCMVSport 2.0
H0486	Hodgkin"s Lymphoma II	Hodgkin"s Lymphoma II			disease	pCMVSport 2.0
H0487	Human Tonsils, lib I	Human Tonsils				pCMVSport 2.0
H0488	Human Tonsils, Lib 2	Human Tonsils				pCMVSport

						2.0
H0494	Keratinocyte	Keratinocyte				pCMVSport 2.0
H0506	Ulcerative Colitis	Colon	Colon			pSport1
H0510	Human Liver, normal	Human Liver, normal, Patient # 8	Liver			pCMVSport 3.0
H0518	pBMC stimulated w/ poly I/C	pBMC stimulated with poly I/C				pCMVSport 3.0
H0521	Primary Dendritic Cells, lib 1	Primary Dendritic cells				pCMVSport 3.0
H0522	Primary Dendritic cells,frac 2	Primary Dendritic cells				pCMVSport 3.0
H0524	Primary Dendritic Cells, CapFinder, frac 2	Primary Dendritic cells				pSport1
H0529	Myoloid Progenitor Cell Line	TF-1 Cell Line; Myoloid progenitor cell line				pCMVSport 3.0
H0537	H. Primary Dendritic Cells,lib 3	Primary Dendritic cells				pCMVSport 2.0
H0542	T Cell helper I	Helper T cell				pCMVSport 3.0
H0543	T cell helper II	Helper T cell				pCMVSport 3.0
H0545	Human endometrial stromal cells-treated with progesterone	Human endometrial stromal cells-treated with proge				pCMVSport 3.0
H0551	Human Thymus Stromal Cells	Human Thymus Stromal Cells				pCMVSport 3.0
H0552	Signal trap,Femur Bone Marrow,pooled	Femur Bone marrow, pooled from 8 male/female				Other
H0556	Activated T-cell(12h)/Thiouridine-re-excision	T-Cells	Blood	Cell Line		Uni-ZAP XR
H0560	KMH2	KMH2				pCMVSport 3.0
H0575	Human Adult Pulmonary;re-excision	Human Adult Pulmonary	Lung			Uni-ZAP XR
H0576	Resting T-Cell; re-excision	T-Cells	Blood	Cell Line		Lambda ZAP II
H0578	Human Fetal Thymus	Fetal Thymus	Thymus			pSport1
H0580	Dendritic cells, pooled	Pooled dendritic cells				pCMVSport 3.0
H0581	Human Bone Marrow, treated	Human Bone Marrow	Bone Marrow			pCMVSport 3.0
H0583	B Cell lymphoma	B Cell Lymphoma	B Cell		disease	pCMVSport 3.0
H0584	Activated T-cells, 24 hrs,re-excision	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0585	Activated T-Cells,12 hrs,re-excision	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0589	CD34 positive cells (cord blood),re-ex	CD34 Positive Cells	Cord Blood			ZAP Express
H0591	Human T-cell lymphoma;re-excision	T-Cell Lymphoma	T-Cell		disease	Uni-ZAP XR
H0606	Human Primary Breast Cancer;re-excision	Human Primary Breast Cancer	Breast		disease	Uni-ZAP XR
H0607	H.Leukocytes, normalized cot 50A3	H.Leukocytes				pCMVSport 1
H0608	H. Leukocytes, control	H.Leukocytes				pCMVSport 1
H0609	H. Leukocytes,	H.Leukocytes				pCMVSport

	normalized cot > 500A					1
H0610	H. Leukocytes, normalized cot 5A	H.Leukocytes				pCMVSport 1
H0611	H. Leukocytes, normalized cot 500 B	H.Leukocytes				pCMVSport 1
H0612	H.Leukocytes, normalized cot 50 B	H.Leukocytes				pCMVSport 1
H0614	H. Leukocytes, normalized cot 500 A	H.Leukocytes				pCMVSport 1
H0625	Ku 812F Basophils Line	Ku 812F Basophils				pSport1
H0635	Human Activated T-Cells, re-excision .	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0637	Dendritic Cells From CD34 Cells	Dentritic cells from CD34 cells				pSport1
H0638	CD40 activated monocyte dendridic cells	CD40 activated monocyte dendridic cells				pSport1
H0641	LPS activated derived dendritic cells	LPS activated monocyte derived dendritic cells				pSport1
H0650	B-Cells	B-Cells				pCMVSport 3.0
H0653	Stromal Cells	Stromal Cells				pSport1
H0656	B-cells (unstimulated)	B-cells (unstimulated)				pSport1
H0657	B-cells (stimulated)	B-cells (stimulated)				pSport1
H0659	Ovary, Cancer (15395A1F): Grade II Papillary Carcinoma	Grade II Papillary Carcinoma, Ovary	Ovary		disease	pSport1
H0660	Ovary, Cancer: (15799A1F) Poorly differentiated carcinoma	Poorly differentiated carcinoma, ovary			disease	pSport1
H0673	Human Prostate Cancer, Stage B2; re-excision	Human Prostate Cancer, stage B2	Prostate			Uni-ZAP XR
H0677	TNFR degenerate oligo	B-Cells				PCRII
H0679	screened clones from Tonsil library	Human Tonsils				Other
S0002	Monocyte activated	Monocyte-activated	blood	Cell Line		Uni-ZAP XR
S0026	Stromal cell TF274	stromal cell	Bone marrow	Cell Line		Uni-ZAP XR
S0027	Smooth muscle, serum treated	Smooth muscle	Pulmanary artery	Cell Line		Uni-ZAP XR
S0031	Spinal cord	Spinal cord	spinal cord			Uni-ZAP XR
S0052	neutrophils control	human neutrophils	blood	Cell Line		Uni-ZAP XR
S0053	Neutrophils IL-1 and LPS induced	human neutrophil induced	blood	Cell Line		Uni-ZAP XR
S0114	Anergic T-cell	Anergic T-cell		Cell Line		Uni-ZAP XR
S0116	Bone marrow	Bone marrow	Bone marrow			Uni-ZAP XR
S0134	Apoptotic T-cell	apoptotic cells		Cell Line		Uni-ZAP XR
S0140	eosinophil-IL5 induced	eosinophil	lung	Cell Line		Uni-ZAP XR
S0142	Macrophage-oxLDL	macrophage-oxidized LDL treated	blood	Cell Line		Uni-ZAP XR
S0144	Macrophage (GM-CSF treated)	Macrophage (GM-CSF treated)				Uni-ZAP XR

S0180	Bone Marrow Stroma, TNF&LPS ind	Bone Marrow Stroma, TNF & LPS induced			disease	Uni-ZAP XR
S0182	Human B Cell 8866	Human B- Cell 8866				Uni-ZAP XR
S0196	Synovial IL-1/TNF stimulated	Synovial Fibroblasts				pSport1
S0212	Bone Marrow Stromal Cell, untreated	Bone Marrow Stromal Cell,untreated				pSport1
S0216	Neutrophils IL-1 and LPS induced	human neutrophil induced	blood	Cell Line		Uni-ZAP XR
S0218	Apoptotic T-cell, re-excision	apoptotic cells		Cell Line		Uni-ZAP XR
S0222	H. Frontal cortex,epileptic;re-excision	H. Brain, Frontal Cortex, Epileptic	Brain		disease	Uni-ZAP XR
S0278	H Macrophage (GM-CSF treated), re-excision	Macrophage (GM-CSF treated)				Uni-ZAP XR
S0282	Brain Frontal Cortex, re-excision	Brain frontal cortex	Brain			Lambda ZAP II
S0292	Osteoarthritis (OA-4)	Human Osteoarthritic Cartilage	Bone		disease	pSport1
S0298	Bone marrow stroma,treated	Bone marrow stroma,treatedSB	Bone marrow			pSport1
S0308	Spleen/normal	Spleen normal				pSport1
S0314	Human osteoarthritis;fraction I	Human osteoarthritic cartilage			disease	pSport1
S0344	Macrophage-oxLDL; re-excision	macrophage-oxidized LDL treated	blood	Cell Line		Uni-ZAP XR
S0358	Colon Normal III	Colon Normal	Colon			pSport1
S0418	CHME Cell Line;treated 5 hrs	CHME Cell Line; treated				pCMVSport 3.0
S0426	Monocyte activated; re-excision	Monocyte-activated	blood	Cell Line		Uni-ZAP XR
S0428	Neutrophils control; re-excision	human neutrophils	blood	Cell Line		Uni-ZAP XR
S0442	Colon Normal	Colon Normal				pSport1
S0452	Thymus	Thymus				pSport1
S0474	Human blood platelets	Platelets	Blood platelets			Other
S3016	Basophil	Basophil				Uni-ZAP XR
S3018	TH1 cells	TH1 cells				Uni-ZAP XR
S3020	TH2 cells	TH2 cells				Uni-ZAP XR
S6028	Human Manic Depression Tissue	Human Manic depression tissue	Brain		disease	Uni-ZAP XR
T0002	Activated T-cells	Activated T-Cell, PBL fraction	Blood	Cell Line		pBluescript SK-
T0041	Jurkat T-cell G1 phase	Jurkat T-cell				pBluescript SK-
T0042	Jurkat T-Cell, S phase	Jurkat T-Cell Line				pBluescript SK-
T0071	Human Bone Marrow	Human Bone Marrow				pBluescript SK-
L0002	Atrium cDNA library Human heart					

L0004	ClonTech HL 1065a					
L0005	Clontech human aorta polyA+ mRNA (#6572)					
L0017	Human (J. Swensen)					
L0020	Human activated dendritic cell mRNA					
L0021	Human adult (K.Okubo)					
L0036	Human chromosome 21q22 mRNA					
L0040	Human colon mucosa					
L0041	Human epidermal keratinocyte					
L0051	Human mRNA (Tripodis and Ragoussis)					
L0055	Human promyelocyte					
L0060	Human thymus NSTH II					
L0065	Liver HepG2 cell line.					
L0070	Selected chromosome 21 cDNA library					
L0109	Human brain cDNA	brain				
L0142	Human placenta cDNA (TFujiwara)	placenta				
L0143	Human placenta polyA+ (TFujiwara)	placenta				
L0157	Human fetal brain (TFujiwara)		brain			
L0163	Human heart cDNA (YNakamura)		heart			
L0171	Human lung adenocarcinoma A549	lung adenocarcinoma		A549		
L0177	Human newborn melanocytes (T.Vogt)			Clonetics Corp. (San Diego, CA) strain #68 and 2486		
L0239	Homo sapiens brain fetus	brain				
L0307	Human C3-A11N			C3-A11N; clonally related variant of OCI LY8-C3P		
L0309	Human E8CASS	breast adenocarcinoma		E8CASS; variant of MCF7		
L0352	Normalized infant brain, Bento Soares					BA, M13-derived
L0361	Stratagene ovary (#937217)		ovary			Bluescript SK
L0362	Stratagene ovarian cancer (#937219)					Bluescript SK-
L0363	NCI_CGAP_GC2	germ cell tumor				Bluescript SK-
L0365	NCI_CGAP_Phe1	pheochromocytoma				Bluescript SK-
L0366	Stratagene schizo brain S11	schizophrenic brain S-11 frontal lobe				Bluescript SK-
L0367	NCI_CGAP_Sch1	Schwannoma tumor				Bluescript SK-

L0368	NCI_CGAP_SS1	synovial sarcoma				Bluescript SK-
L0369	NCI_CGAP_AA1	adrenal adenoma	adrenal gland			Bluescript SK-
L0370	Johnston frontal cortex	pooled frontal lobe	brain			Bluescript SK-
L0375	NCI_CGAP_Kid6	kidney tumor	kidney			Bluescript SK-
L0376	NCI_CGAP_Lar1	larynx	larynx			Bluescript SK-
L0377	NCI_CGAP_HN2	squamous cell carcinoma from vocal cord	larynx			Bluescript SK-
L0378	NCI_CGAP_Lu1	lung tumor	lung			Bluescript SK-
L0381	NCI_CGAP_HN4	squamous cell carcinoma	pharynx			Bluescript SK-
L0383	NCI_CGAP_Pr24	invasive tumor (cell line)	prostate			Bluescript SK-
L0384	NCI_CGAP_Pr23	prostate tumor	prostate			Bluescript SK-
L0385	NCI_CGAP_Gas1	gastric tumor	stomach			Bluescript SK-
L0386	NCI_CGAP_HN3	squamous cell carcinoma from base of tongue	tongue			Bluescript SK-
L0387	NCI_CGAP_GCB0	germinal center B-cells	tonsil			Bluescript SK-
L0389	NCI_CGAP_HN5	normal gingiva (cell line from primary keratinocyt				Bluescript SK-
L0394	H, Human adult Brain Cortex tissue					gt11
L0415	b4HB3MA Cot8-HAP-Ft					Lafmid BA
L0435	Infant brain, LLNL array of Dr. M. Soares 1NIB					lafmid BA
L0438	normalized infant brain cDNA	total brain	brain			lafmid BA
L0439	Soares infant brain 1NIB		whole brain			Lafmid BA
L0451	N3HFLSK20					Lafmid K
L0452	Chromosome 21, K. Gardiner					Lambda
L0455	Human retina cDNA randomly primed sublibrary	retina	eye			lambda gt10
L0456	Human retina cDNA Tsp509I-cleaved sublibrary	retina	eye			lambda gt10
L0457	multi-tissue normalized short-fragment	multi-tissue	pooled			lambda gt10
L0459	Adult heart, Clontech					Lambda gt11
L0462	WATM1					lambda gt11
L0465	TEST1, Human adult Testis tissue					lambda nm1149
L0468	HE6W					lambda zap
L0471	Human fetal heart, Lambda ZAP Express					Lambda ZAP Express
L0475	KG1-a Lambda Zap Express cDNA library			KG1-a		Lambda Zap Express (Stratagene)
L0476	Fetal brain, Stratagene					Lambda ZAP II

L0480	Stratagene cat#937212 (1992)					Lambda ZAP, pBluescript SK(-)
L0481	CD34+DIRECTIONAL					Lambda ZAPII
L0483	Human pancreatic islet					Lambda ZAPII
L0485	STRATAGENE Human skeletal muscle cDNA library, cat. #936215.	skeletal muscle	leg muscle			Lambda ZAPII
L0492	Human Genomic					pAMP
L0493	NCI_CGAP_Ov26	papillary serous carcinoma	ovary			pAMP1
L0498	NCI_CGAP_HSC3	CD34+, T negative, patient with chronic myelogenou	bone marrow			pAMP1
L0506	NCI_CGAP_Br16	lobullar carcinoma in situ	breast			pAMP1
L0508	NCI_CGAP_Lu25	bronchioalveolar carcinoma	lung			pAMP1
L0509	NCI_CGAP_Lu26	invasive adenocarcinoma	lung			pAMP1
L0512	NCI_CGAP_Ov36	borderline ovarian carcinoma	ovary			pAMP1
L0513	NCI_CGAP_Ov37	early stage papillary serous carcinoma	ovary			pAMP1
L0515	NCI_CGAP_Ov32	papillary serous carcinoma	ovary			pAMP1
L0517	NCI_CGAP_Pr1					pAMP10
L0518	NCI_CGAP_Pr2					pAMP10
L0519	NCI_CGAP_Pr3					pAMP10
L0520	NCI_CGAP_Alv1	alveolar rhabdomyosarcoma				pAMP10
L0521	NCI_CGAP_Ew1	Ewing"s sarcoma				pAMP10
L0523	NCI_CGAP_Lip2	liposarcoma				pAMP10
L0526	NCI_CGAP_Pr12	metastatic prostate bone lesion				pAMP10
L0527	NCI_CGAP_Ov2	ovary				pAMP10
L0528	NCI_CGAP_Pr5	prostate				pAMP10
L0529	NCI_CGAP_Pr6	prostate				pAMP10
L0530	NCI_CGAP_Pr8	prostate				pAMP10
L0532	NCI_CGAP_Thy1	thyroid				pAMP10
L0534	Chromosome 7 Fetal Brain cDNA Library	brain	brain			pAMP10
L0535	NCI_CGAP_Br5	infiltrating ductal carcinoma	breast			pAMP10
L0539	Chromosome 7 Placental cDNA Library		placenta			pAMP10
L0541	NCI_CGAP_Pr7	low-grade prostatic neoplasia	prostate			pAMP10
L0542	NCI_CGAP_Pr11	normal prostatic epithelial cells	prostate			pAMP10
L0543	NCI_CGAP_Pr9	normal prostatic epithelial cells	prostate			pAMP10
L0545	NCI_CGAP_Pr4.1	prostatic intraepithelial neoplasia - high grade	prostate			pAMP10
L0546	NCI_CGAP_Pr18	stroma	prostate			pAMP10
L0547	NCI_CGAP_Pr16	tumor	prostate			pAMP10
L0551	NCI_CGAP_HN7	normal squamous				pAMP10

		epithelium, floor of mouth				
L0556	NCI_CGAP_Lu34.1	large cell carcinoma	lung			pAMP10
L0562	Chromosome 7 HeLa cDNA Library			HeLa cell line; ATCC		pAMP10
L0565	Normal Human Trabecular Bone Cells	Bone	Hip			pBluescript
L0581	Stratagene liver (#937224)		liver			pBluescript SK
L0586	HTCDL1					pBluescript SK(-)
L0588	Stratagene endothelial cell 937223					pBluescript SK-
L0589	Stratagene fetal retina 937202					pBluescript SK-
L0590	Stratagene fibroblast (#937212)					pBluescript SK-
L0591	Stratagene HeLa cell s3 937216					pBluescript SK-
L0592	Stratagene hNT neuron (#937233)					pBluescript SK-
L0593	Stratagene neuroepithelium (#937231)					pBluescript SK-
L0594	Stratagene neuroepithelium NT2RAMI 937234					pBluescript SK-
L0595	Stratagene NT2 neuronal precursor 937230	neuroepithelial cells	brain			pBluescript SK-
L0596	Stratagene colon (#937204)		colon			pBluescript SK-
L0597	Stratagene corneal stroma (#937222)		cornea			pBluescript SK-
L0598	Morton Fetal Cochlea	cochlea	ear			pBluescript SK-
L0599	Stratagene lung (#937210)		lung			pBluescript SK-
L0600	Weizmann Olfactory Epithelium	olfactory epithelium	nose			pBluescript SK-
L0601	Stratagene pancreas (#937208)		pancreas			pBluescript SK-
L0602	Pancreatic Islet	pancreatic islet	pancreas			pBluescript SK-
L0603	Stratagene placenta (#937225)		placenta			pBluescript SK-
L0604	Stratagene muscle 937209	muscle	skeletal muscle			pBluescript SK-
L0605	Stratagene fetal spleen (#937205)	fetal spleen	spleen			pBluescript SK-
L0606	NCI_CGAP_Lym5	follicular lymphoma	lymph node			pBluescript SK-
L0607	NCI_CGAP_Lym6	mantle cell lymphoma	lymph node			pBluescript SK-
L0608	Stratagene lung carcinoma 937218	lung carcinoma	lung	NCI-H69		pBluescript SK-
L0612	Schiller oligodendroglioma	oligodendroglioma	brain			pBluescript SK- (Stratagene)
L0617	Chromosome 22 exon					pBluescriptII KS+
L0619	Chromosome 9 exon II					pBluescriptII

						KS+
L0622	HM1					pcDNAII (Invitrogen)
L0623	HM3	pectoral muscle (after mastectomy)				pcDNAII (Invitrogen)
L0626	NCI_CGAP_GC1	bulk germ cell seminoma				pCMV-SPORT2
L0629	NCI_CGAP_Mel3	metastatic melanoma to bowel	bowel (skin primary)			pCMV-SPORT4
L0631	NCI_CGAP_Br7		breast			pCMV-SPORT4
L0633	NCI_CGAP_Lu6	small cell carcinoma	lung			pCMV-SPORT4
L0634	NCI_CGAP_Ov8	serous adenocarcinoma	ovary			pCMV-SPORT4
L0635	NCI_CGAP_PNS1	dorsal root ganglion	peripheral nervous system			pCMV-SPORT4
L0637	NCI_CGAP_Brn53	three pooled meningiomas	brain			pCMV-SPORT6
L0638	NCI_CGAP_Brn35	tumor, 5 pooled (see description)	brain			pCMV-SPORT6
L0639	NCI_CGAP_Brn52	tumor, 5 pooled (see description)	brain			pCMV-SPORT6
L0640	NCI_CGAP_Br18	four pooled high-grade tumors, including two prima	breast			pCMV-SPORT6
L0641	NCI_CGAP_Co17	juvenile granulosa tumor	colon			pCMV-SPORT6
L0643	NCI_CGAP_Co19	moderately differentiated adenocarcinoma	colon			pCMV-SPORT6
L0644	NCI_CGAP_Co20	moderately differentiated adenocarcinoma	colon			pCMV-SPORT6
L0645	NCI_CGAP_Co21	moderately differentiated adenocarcinoma	colon			pCMV-SPORT6
L0646	NCI_CGAP_Co14	moderately-differentiated adenocarcinoma	colon			pCMV-SPORT6
L0647	NCI_CGAP_Sar4	five pooled sarcomas, including myxoid liposarcoma	connective tissue			pCMV-SPORT6
L0648	NCI_CGAP_Eso2	squamous cell carcinoma	esophagus			pCMV-SPORT6
L0649	NCI_CGAP_GU1	2 pooled high-grade transitional cell tumors	genitourinary tract			pCMV-SPORT6
L0651	NCI_CGAP_Kid8	renal cell tumor	kidney			pCMV-SPORT6
L0652	NCI_CGAP_Lu27	four pooled poorly-differentiated adenocarcinomas	lung			pCMV-SPORT6
L0653	NCI_CGAP_Lu28	two pooled squamous cell carcinomas	lung			pCMV-SPORT6
L0654	NCI_CGAP_Lu31		lung, cell line			pCMV-SPORT6
L0655	NCI_CGAP_Lym12	lymphoma, follicular mixed small and large cell	lymph node			pCMV-SPORT6
L0656	NCI_CGAP_Ov38	normal epithelium	ovary			pCMV-

						SPORT6
L0657	NCI_CGAP_Ov23	tumor, 5 pooled (see description)	ovary			pCMV-SPORT6
L0658	NCI_CGAP_Ov35	tumor, 5 pooled (see description)	ovary			pCMV-SPORT6
L0659	NCI_CGAP_Pan1	adenocarcinoma	pancreas			pCMV-SPORT6
L0661	NCI_CGAP_Mel15	malignant melanoma, metastatic to lymph node	skin			pCMV-SPORT6
L0662	NCI_CGAP_Gas4	poorly differentiated adenocarcinoma with signet r	stomach			pCMV-SPORT6
L0663	NCI_CGAP_Ut2	moderately-differentiated endometrial adenocarcino	uterus			pCMV-SPORT6
L0664	NCI_CGAP_Ut3	poorly-differentiated endometrial adenocarcinoma,	uterus			pCMV-SPORT6
L0665	NCI_CGAP_Ut4	serous papillary carcinoma, high grade, 2 pooled t	uterus			pCMV-SPORT6
L0666	NCI_CGAP_Ut1	well-differentiated endometrial adenocarcinoma, 7	uterus			pCMV-SPORT6
L0667	NCI_CGAP_CML1	myeloid cells, 18 pooled CML cases, BCR/ABL rearra	whole blood			pCMV-SPORT6
L0682	Stanley Frontal NB pool 2	frontal lobe (see description)	brain			pCR2.1-TOPO (Invitrogen)
L0686	Stanley Frontal SN pool 2	frontal lobe (see description)	brain			pCR2.1-TOPO (Invitrogen)
L0697	Testis 1					PGEM 5zf(+)
L0700	Outward Alu-primed hncDNA library					pGEM-3Z
L0717	Gessler Wilms tumor					pSPORT1
L0720	PN001-Normal Human Prostate		prostate			pSport1
L0731	Soares_pregnant_uterus_NbHPU		uterus			pT7T3-Pac
L0738	Human colorectal cancer					pT7T3D
L0740	Soares melanocyte 2NbHM	melanocyte				pT7T3D (Pharmacia) with a modified polylinker
L0741	Soares adult brain N2b4HB55Y		brain			pT7T3D (Pharmacia) with a modified polylinker
L0742	Soares adult brain N2b5HB55Y		brain			pT7T3D (Pharmacia) with a modified polylinker
L0743	Soares breast 2NbHBst		breast			pT7T3D (Pharmacia)

						with a modified polylinker
L0744	Soares breast 3NbHBst		breast			pT7T3D (Pharmacia) with a modified polylinker
L0745	Soares retina N2b4HR	retina	eye			pT7T3D (Pharmacia) with a modified polylinker
L0746	Soares retina N2b5HR	retina	eye			pT7T3D (Pharmacia) with a modified polylinker
L0747	Soares_fetal_heart_NbHH 19W		heart			pT7T3D (Pharmacia) with a modified polylinker
L0748	Soares fetal liver spleen 1NFLS		Liver and Spleen			pT7T3D (Pharmacia) with a modified polylinker
L0749	Soares_fetal_liver_spleen _1NFLS_S1		Liver and Spleen			pT7T3D (Pharmacia) with a modified polylinker
L0750	Soares_fetal_lung_NbHL1 9W		lung			pT7T3D (Pharmacia) with a modified polylinker
L0751	Soares ovary tumor NbHOT	ovarian tumor	ovary			pT7T3D (Pharmacia) with a modified polylinker
L0752	Soares_parathyroid_tumor _NbHPA	parathyroid tumor	parathyroid gland			pT7T3D (Pharmacia) with a modified polylinker
L0753	Soares_pineal_gland_N3H PG		pineal gland			pT7T3D (Pharmacia) with a modified polylinker
L0754	Soares placenta Nb2HP		placenta			pT7T3D (Pharmacia) with a modified polylinker
L0755	Soares_placenta_8to9wee ks_2NbHP8to9W		placenta			pT7T3D (Pharmacia) with a modified polylinker

L0756	Soares_multiple_sclerosis_2NbHMSP	multiple sclerosis lesions				pT7T3D (Pharmacia) with a modified polylinker V_TYPE
L0757	Soares_senescent_fibroblasts_NbHSF	senescent fibroblast				pT7T3D (Pharmacia) with a modified polylinker V_TYPE
L0758	Soares_testis_NHT					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0759	Soares_total_fetus_Nb2HF8_9w					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0761	NCI_CGAP_CLL1	B-cell, chronic lymphotic leukemia				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0762	NCI_CGAP_Br1.1	breast				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0763	NCI_CGAP_Br2	breast				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0764	NCI_CGAP_Co3	colon				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0766	NCI_CGAP_GCB1	germinal center B cell				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0767	NCI_CGAP_GC3	pooled germ cell tumors				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0768	NCI_CGAP_GC4	pooled germ cell tumors				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0769	NCI_CGAP_Brn25	anaplastic oligodendroglioma	brain			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0770	NCI_CGAP_Brn23	glioblastoma (pooled)	brain			pT7T3D-Pac (Pharmacia)

						with a modified polylinker
L0771	NCI_CGAP_Co8	adenocarcinoma	colon			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0772	NCI_CGAP_Co10	colon tumor RER+	colon			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0773	NCI_CGAP_Co9	colon tumor RER+	colon			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0774	NCI_CGAP_Kid3		kidney			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0775	NCI_CGAP_Kid5	2 pooled tumors (clear cell type)	kidney			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0776	NCI_CGAP_Lu5	carcinoid	lung			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0777	Soares_NhHMPu_S1	Pooled human melanocyte, fetal heart, and pregnant	mixed (see below)			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0779	Soares_NFL_T_GBC_S1		pooled			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0780	Soares_NSF_F8_9W_OT_PA_P_S1		pooled			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0783	NCI_CGAP_Pr22	normal prostate	prostate			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0784	NCI_CGAP_Lei2	leiomyosarcoma	soft tissue			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0785	Barstead spleen HPLRB2		spleen			pT7T3D-Pac (Pharmacia) with a modified polylinker

L0786	Soares_NbHFB		whole brain			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0787	NCI_CGAP_Sub1					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0788	NCI_CGAP_Sub2					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0789	NCI_CGAP_Sub3					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0790	NCI_CGAP_Sub4					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0791	NCI_CGAP_Sub5					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0792	NCI_CGAP_Sub6					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0794	NCI_CGAP_GC6	pooled germ cell tumors				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0796	NCI_CGAP_Brn50	medulloblastoma	brain			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0800	NCI_CGAP_Co16	colon tumor, RER+	colon			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0803	NCI_CGAP_Kid11		kidney			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0804	NCI_CGAP_Kid12	2 pooled tumors (clear cell type)	kidney			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0805	NCI_CGAP_Lu24	carcinoid	lung			pT7T3D-Pac (Pharmacia) with a modified

						polylinker
L0806	NCI_CGAP_Lu19	squamous cell carcinoma, poorly differentiated (4	lung			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0809	NCI_CGAP_Pr28		prostate			pT7T3D-Pac (Pharmacia) with a modified polylinker
L2245	NEM subtracted human fetal kidney cDNA					pUEX1
L2250	Human cerebral cortex	cerebral cortex				
L2251	Human fetal lung	Fetal lung				

TABLE 5

OMIM Reference	Description
100678	ACAT2 deficiency
102578	Leukemia, acute promyelocytic, PML/RARA type
102770	Myoadenylate deaminase deficiency
103000	Hemolytic anemia due to adenylate kinase deficiency
103050	Autism, succinylpurinemic
103050	Adenylosuccinase deficiency
103600	[Dysalbuminemic hyperthyroxinemia]
103600	[Dysalbuminemic hyperzincemia], 194470
103600	Analbuminemia
103850	Aldolase A deficiency
104150	[AFP deficiency, congenital]
104150	[Hereditary persistence of alpha-fetoprotein]
104170	NAGA deficiency, mild
104170	Schindler disease
104170	Kanzaki disease
104311	Alzheimer disease-3
104500	Amelogenesis imperfecta-2, hypoplastic local type
104770	Amyloidosis, secondary, susceptibility to
105580	Anal canal carcinoma
106165	Hypertension, essential, 145500
106300	Ankylosing spondylitis
107280	Cerebrovascular disease, occlusive
107280	Alpha-1-antichymotrypsin deficiency
107300	Antithrombin III deficiency
107400	Emphysema
107400	Emphysema-cirrhosis
107470	Atypical mycobacterial infection, familial disseminated, 209950
107470	BCG infection, generalized familial
107470	Tuberculosis, susceptibility to
107670	Apolipoprotein A-II deficiency
107741	Hyperlipoproteinemia, type III
107777	Diabetes insipidus, nephrogenic, autosomal recessive, 222000
108725	Atherosclerosis, susceptibility to
108730	Brody myopathy, 601003
108800	Atrial septal defect, secundum type
108962	Hypertension, salt-resistant
108985	Atrophia areata
109150	Machado-Joseph disease
109270	Renal tubular acidosis, distal, 179800
109270	Spherocytosis, hereditary
109270	[Acanthocytosis, one form]
109270	[Elliptocytosis, Malaysian-Melanesian type]

109270	Hemolytic anemia due to band 3 defect
109560	Leukemia/lymphoma, B-cell, 3
109690	Asthma, nocturnal, susceptibility to
109690	Obesity, susceptibility to
109700	Hemodialysis-related amyloidosis
110700	Vivax malaria, susceptibility to
113705	Ovarian cancer
113705	Breast cancer-1
113721	Breast cancer
113900	Heart block, progressive familial, type I
114208	Malignant hyperthermia susceptibility 5, 601887
114208	Hypokalemic periodic paralysis, 170400
114350	Leukemia, acute myeloid
114835	Monocyte carboxyesterase deficiency
115470	Cat eye syndrome
116800	Cataract, Marner type
116860	Cavernous angiomatous malformations
117700	[Hypoceruloplasminemia, hereditary]
117700	Hemosiderosis, systemic, due to aceruloplasminemia
118210	Charcot-Marie-Tooth neuropathy-2A
118485	Polycystic ovary syndrome with hyperandrogenemia
119300	van der Woude syndrome
120110	Metaphyseal chondrodysplasia, Schmid type
120215	Ehlers-Danlos syndrome, type I, 130000
120215	Ehlers-Danlos syndrome, type II, 130010
120220	Bethlem myopathy, 158810
120240	Bethlem myopathy, 158810
120260	Epiphyseal dysplasia, multiple, type 2, 600204
120280	Stickler syndrome, type III
120280	Marshall syndrome, 154780
120290	OSMED syndrome, 215150
120290	Stickler syndrome, type II, 184840
120435	Muir-Torre syndrome, 158320
120435	Colorectal cancer, hereditary, nonpolyposis, type 1 Ovarian cancer
120550	C1q deficiency, type A
120570	C1q deficiency, type B
120575	C1q deficiency, type C
120620	SLE susceptibility
120620	CR1 deficiency
120700	C3 deficiency
120810	C4 deficiency
120820	C4 deficiency
120900	C5 deficiency
120920	Measles, susceptibility to
120940	C9 deficiency

120950	C8 deficiency, type I
120960	C8 deficiency, type II
121011	Deafness, autosomal dominant 3, 601544
121011	Deafness, autosomal recessive 1, 220290
121014	Heterotaxia, visceroatrial, autosomal recessive
121360	Myeloid leukemia, acute, M4Eo subtype
121700	Congenital hereditary endothelial dystrophy of cornea
121800	Corneal dystrophy, crystalline, Schnyder
122000	Corneal dystrophy, posterior polymorphous
122500	[Transcortin deficiency]
122560	ACTH deficiency, 201400
122720	Nicotine addiction, protection from
122720	Coumarin resistance, 122700
123000	Craniometaphyseal dysplasia
123101	Craniosynostosis, type 2
123270	[Creatine kinase, brain type, ectopic expression of]
123580	Cataract, congenital, autosomal dominant
123620	Cataract, cerulean, type 2, 601547
123829	Melanoma
123940	White sponge nevus, 193900
124030	Parkinsonism, susceptibility to
124030	Debrisoquine sensitivity
124200	Darier disease (keratosis follicularis)
125490	Dentinogenesis imperfecta-1
125852	Insulin-dependent diabetes mellitus-2
126060	Anemia, megaloblastic, due to DHFR deficiency
126340	Xeroderma pigmentosum, group D, 278730
126391	DNA ligase I deficiency
126452	Autonomic nervous system dysfunction
126452	[Novelty seeking personality]
126600	Drusen, radial, autosomal dominant
126650	Chloride diarrhea, congenital, Finnish type, 214700
126650	Colon cancer
129490	Ectodermal dysplasia-3, anhidrotic
129500	Ectodermal dysplasia, hidrotic
129900	EEC syndrome-1
130410	Glutaricaciduria, type IIB
130500	Elliptocytosis-1
130650	Beckwith-Wiedemann syndrome
131195	Hereditary hemorrhagic telangiectasia-1, 187300
131210	Atherosclerosis, susceptibility to
131400	Eosinophilia, familial
132700	Cylindromatosis
133170	Erythremia
133171	[Erythrocytosis, familial], 133100
133200	Erythrokeratodermia variabilis

133780	Vitreoretinopathy, exudative, familial
134370	Factor H deficiency
134370	Hemolytic-uremic syndrome, 235400
134370	Membroproliferative glomerulonephritis
134570	Factor XIIIA deficiency
134580	Factor XIIIB deficiency
134790	Hyperferritinemia-cataract syndrome, 600886
135300	Fibromatosis, gingival
135940	Ichthyosis vulgaris, 146700
136132	[Fish-odor syndrome], 602079
136435	Ovarian dysgenesis, hypergonadotropic, with normal karyotype, 233300
136550	Macular dystrophy, North Carolina type
136836	Fucosyltransferase-6 deficiency
137600	Iridogoniodysgenesis syndrome
138079	Hyperinsulinism, familial, 602485
138079	MODY, type 2, 125851
138140	Glucose transport defect, blood-brain barrier
138190	Diabetes mellitus, noninsulin-dependent
138491	Startle disease, autosomal recessive
138491	Startle disease/hyperekplexia, autosomal dominant, 149400
138491	Hyperekplexia and spastic paraparesis
138570	Non-insulin dependent diabetes mellitus, susceptibility to
138971	Kostmann neutropenia, 202700
138981	Pulmonary alveolar proteinosis, 265120
139190	Gigantism due to GHRF hypersecretion
139190	Isolated growth hormone deficiency due to defect in GHRF
139191	Growth hormone deficient dwarfism
139330	Night blindness, congenital stationary
139350	Epidermolytic hyperkeratosis, 113800
139350	Keratoderma, palmoplantar, nonepidermolytic
139360	Pituitary ACTH-secreting adenoma
140100	[Anhaptoglobinemia]
140100	[Hypohaptogloginemia]
141900	Methemoglobinemias, beta-
141900	Sickle cell anemia
141900	Thalassemias, beta-
141900	Erythremias, beta-
141900	HPFH, deletion type
141900	Heinz body anemias, beta-
142000	Thalassemia due to Hb Lepore
142000	Thalassemia, delta-
142200	HPFH, nondeletion type A
142250	HPFH, nondeletion type G
142270	Hereditary persistence of fetal hemoglobin
142360	Thrombophilia due to heparin cofactor II deficiency

142470	[Hereditary persistence of fetal hemoglobin, heterocellular]
142857	Pemphigoid, susceptibility to
142858	Beryllium disease, chronic, susceptibility to
142959	Hand-foot-uterus syndrome, 140000
143200	Wagner syndrome
143200	Erosive vitreoretinopathy
143890	Hypercholesterolemia, familial
144200	Epidermolytic palmoplantar keratoderma
145001	Hyperparathyroidism-jaw tumor syndrome
145260	Pseudohypoaldosteronism, type II
145981	Hypocalciuric hypercalcemia, type II
146760	[IgG receptor I, phagocytic, familial deficiency of]
146790	Lupus nephritis, susceptibility to
147061	Allergy and asthma susceptibility
147141	Leukemia, acute lymphoblastic
147280	Hepatocellular carcinoma
147440	Growth retardation with deafness and mental retardation
147557	Epidermolysis bullosa, junctional, with pyloric atresia, 226730
147570	Interferon, immune, deficiency
147575	Myelodysplastic syndrome, preleukemic
147575	Myelogenous leukemia, acute
147575	Macrocytic anemia refractory, of 5q- syndrome, 153550
147781	Atopy, susceptibility to
148040	Epidermolysis bullosa simplex, Koebner, Dowling-Meara, and Weber-Cockayne types, 131900, 131760, 131800
148041	Pachyonychia congenita, Jadassohn-Lewandowsky type, 167200
148043	Meesmann corneal dystrophy, 122100
148065	White sponge nevus, 193900
148066	Epidermolysis bullosa simplex, Koebner, Dowling-Meara, and Weber-Cockayne types, 131900, 131760, 131800
148066	Epidermolysis bullosa simplex, recessive, 601001
148067	Nonepidermolytic palmoplantar keratoderma, 600962
148067	Pachyonychia congenita, Jadassohn-Lewandowsky type, 167200
148069	Pachyonychia congenita, Jackson-Lawler type, 167210
148070	Liver disease, susceptibility to, from hepatotoxins or viruses
148080	Epidermolytic hyperkeratosis, 113800
148900	Klippel-Feil syndrome with laryngeal malformation
150000	Exertional myoglobinuria due to deficiency of LDH-A
150210	Lactoferrin-deficient neutrophils, 245480
150240	Cutis laxa, marfanoid neonatal type
150250	Larsen syndrome, autosomal dominant
150270	Laryngeal adductor paralysis
150292	Epidermolysis bullosa, Herlitz junctional type, 226700
150310	Epidermolysis bullosa, Herlitz junctional type, 226700
150310	Epidermolysis bullosa, generalized atrophic benign, 226650
151385	Leukemia, acute myeloid

151410	Leukemia, chronic myeloid
151440	Leukemia, T-cell acute lymphoblastoid
151670	Hepatic lipase deficiency
152200	Coronary artery disease, susceptibility to
152445	Vohwinkel syndrome, 124500
152445	Erythrokeratoderma, progressive symmetric, 602036
152760	Hypogonadotropic hypogonadism due to GNRH deficiency, 227200
152780	Hypogonadism, hypergonadotropic
152780	Male pseudohermaphroditism due to defective LH
152790	Precocious puberty, male, 176410
152790	Leydig cell hypoplasia
153455	Cutis laxa, recessive, type I, 219100
153880	Macular dystrophy, dominant cystoid
154275	Malignant hyperthermia susceptibility 2
154276	Malignant hyperthermia susceptibility 3
154500	Treacher Collins mandibulofacial dysostosis
154550	Carbohydrate-deficient glycoprotein syndrome, type Ib, 602579
156225	Muscular dystrophy, congenital merosin-deficient
157170	Holoprosencephaly-2
157640	PEO with mitochondrial DNA deletions, type 1
159000	Muscular dystrophy, limb-girdle, type 1A
159001	Muscular dystrophy, limb-girdle, type 1B
159440	Charcot-Marie-Tooth neuropathy-1B, 118200
159440	Dejerine-Sottas disease, myelin P-related, 145900
159440	Hypomyelination, congenital
160781	Cardiomyopathy, hypertrophic, mid-left ventricular chamber type
160900	Myotonic dystrophy
162200	Neurofibromatosis, type 1
162200	Watson syndrome, 193520
164040	Leukemia, acute promyelocytic, NPM/RARA type
164200	Oculodentodigital dysplasia
164200	Syndactyly, type III, 186100
164500	Spinocerebellar ataxia-7
164731	Ovarian carcinoma, 167000
164860	Renal cell carcinoma, papillary, familial and sporadic
164953	Liposarcoma
165215	3q21q26 syndrome
165500	Optic atrophy 1
166600	Osteopetrosis, AD, type II
166800	Otosclerosis
167000	Ovarian cancer, serous
167250	Paget disease of bone
167409	Optic nerve coloboma with renal disease, 120330
167415	Hypothyroidism, congenital, due to thyroid dysgenesis or hypoplasia

168360	Paraneoplastic sensory neuropathy
168468	Metaphyseal chondrodysplasia, Murk Jansen type, 156400
168610	Parkinsonism-dementia with pallidopontonigral degeneration
169600	Hailey-Hailey disease
170261	Bare lymphocyte syndrome, type I, due to TAP2 deficiency
170650	Periodontitis, juvenile
170995	Zellweger syndrome-2
171190	Hypertension, essential, 145500
171760	Hypophosphatasia, adult, 146300
171760	Hypophosphatasia, infantile, 241500
171860	Hemolytic anemia due to phosphofructokinase deficiency
172400	Hemolytic anemia due to glucosephosphate isomerase deficiency
172400	Hydrops fetalis, one form
172411	Colorectal cancer, resistance to
172471	Glycogenosis, hepatic, autosomal
172490	Phosphorylase kinase deficiency of liver and muscle, 261750
173350	Plasminogen Tochigi disease
173350	Plasminogen deficiency, types I and II
173350	Thrombophilia, dysplasminogenemic
173360	Thrombophilia due to excessive plasminogen activator inhibitor
173360	Hemorrhagic diathesis due to PAI1 deficiency
173610	Platelet alpha/delta storage pool deficiency
173850	Polio, susceptibility to
174000	Medullary cystic kidney disease, AD
174900	Polyposis, juvenile intestinal
176000	Porphyria, acute intermittent
176100	Porphyria cutanea tarda
176100	Porphyria, hepatoerythropoietic
176705	Breast cancer, sporadic
176730	Diabetes mellitus, rare form
176730	Hyperproinsulinemia, familial
176730	MODY, one form
176830	Obesity, adrenal insufficiency, and red hair
176830	ACTH deficiency
176860	Purpura fulminans, neonatal
176860	Thrombophilia due to protein C deficiency
176943	Apert syndrome, 101200
176943	Pfeiffer syndrome, 101600
176943	Beare-Stevenson cutis gyrata syndrome, 123790
176943	Crouzon craniofacial dysostosis, 123500
176943	Jackson-Weiss syndrome, 123150
176947	Selective T-cell defect
177070	Spherocytosis, hereditary, Japanese type
177070	Hermansky-Pudlak syndrome, 203300
177900	Psoriasis susceptibility-1
178300	Ptosis, hereditary congenital, 1

178640	Pulmonary alveolar proteinosis, congenital, 265120
179450	Ragweed sensitivity
179755	Renal cell carcinoma, papillary, 1
179820	[Hyperproreninemia]
180020	Retinal cone dystrophy-1
180071	Retinitis pigmentosa, autosomal recessive
180100	Retinitis pigmentosa-1
180104	Retinitis pigmentosa-9
180105	Retinitis pigmentosa-10
180250	Retinol binding protein, deficiency of
180297	Anemia, hemolytic, Rh-null, suppressor type, 268150
180380	Night blindness, congenital stationery, rhodopsin-related
180380	Retinitis pigmentosa, autosomal recessive
180380	Retinitis pigmentosa-4, autosomal dominant
180901	Malignant hyperthermia susceptibility 1, 145600
180901	Central core disease, 117000
181405	Scapuloperoneal spinal muscular atrophy, New England type
181430	Scapuloperoneal syndrome, myopathic type
181460	Schistosoma mansoni, susceptibility/resistance to
181510	Schizophrenia
182138	Anxiety-related personality traits
182280	Small-cell cancer of lung
182380	Glucose/galactose malabsorption
182381	Renal glucosuria, 253100
182500	Cataract, congenital
182600	Spastic paraplegia-3A
182601	Spastic paraplegia-4
182860	Pyropoikilocytosis
182860	Spherocytosis, recessive
182860	Elliptocytosis-2
185000	Stomatocytosis I
185430	Atherosclerosis, susceptibility to
185470	Myopathy due to succinate dehydrogenase deficiency
185800	Symphalangism, proximal
186580	Arthrocutaneouveal granulomatosis
186770	Leukemia, T-cell acute lymphocytic
186780	CD3, zeta chain, deficiency
186880	Leukemia/lymphoma, T-cell
186921	Leukemia, T-cell acute lymphoblastic
186960	Leukemia/lymphoma, T-cell
187040	Leukemia-1, T-cell acute lymphoblastic
188040	Thrombophilia due to thrombomodulin defect
188070	Bleeding disorder due to defective thromboxane A2 receptor
188400	Velocardiofacial syndrome, 192430
188400	DiGeorge syndrome
188826	Sorsby fundus dystrophy, 136900

189800	Preeclampsia/eclampsia
189980	Leukemia, chronic myeloid
190000	Atransferrinemia
190020	Bladder cancer, 109800
190040	Dermatofibrosarcoma protuberans
190040	Giant-cell fibroblastoma
190040	Meningioma, SIS-related
190100	Geniospasm
190195	Ichthyosiform erythroderma, congenital, 242100
190195	Ichthyosis, lamellar, autosomal recessive, 242300
190198	Leukemia, T-cell acute lymphoblastic
190685	Down syndrome
190900	Colorblindness, tritan
191030	Nemaline myopathy-1, 161800
191044	Cardiomyopathy, familial hypertrophic
191045	Cardiomyopathy, familial hypertrophic, 2, 115195
191290	Segawa syndrome, recessive
191315	Insensitivity to pain, congenital, with anhidrosis, 256800
192090	Ovarian carcinoma
192090	Breast cancer, lobular
192090	Endometrial carcinoma
192090	Gastric cancer, familial, 137215
192500	Jervell and Lange-Nielsen syndrome, 220400
192500	Long QT syndrome-1
194071	Wilms tumor, type 2
194071	Adrenocortical carcinoma, hereditary, 202300
200150	Choreoacanthocytosis
200350	Acetyl-CoA carboxylase deficiency
201470	Acyl-CoA dehydrogenase, short-chain, deficiency of
201910	Adrenal hyperplasia, congenital, due to 21-hydroxylase deficiency
202200	Glucocorticoid deficiency, due to ACTH unresponsiveness
203310	Ocular albinism, autosomal recessive
203500	Alkaptonuria
204500	Ceroid-lipofuscinosis, neuronal 2, classic late infantile
205900	Anemia, Diamond-Blackfan
207750	Hyperlipoproteinemia, type Ib
207800	Argininemia
208100	Arthrogryposis multiplex congenita, neurogenic
208250	Jacobs syndrome
210900	Bloom syndrome
214400	Charcot-Marie-Tooth neuropathy-4A
216550	Cohen syndrome
216900	Achromatopsia
217000	C2 deficiency
217030	C3b inactivator deficiency

217050	C6 deficiency
217050	Combined C6/C7 deficiency
217070	C7 deficiency
217095	Conotruncal cardiac anomalies
217300	Cornea plana congenita, recessive
217800	Macular corneal dystrophy
218000	Andermann syndrome
218030	Apparent mineralocorticoid excess, hypertension due to
221770	Polycystic lipomembranous osteodysplasia with sclerosing leukencephalopathy
221820	Gliosis, familial progressive subcortical
222100	Diabetes mellitus, insulin-dependent-1
222600	Atelosteogenesis II, 256050
222600	Achondrogenesis Ib, 600972
222600	Diastrophic dysplasia
222700	Lysinuric protein intolerance
222800	Hemolytic anemia due to bisphosphoglycerate mutase deficiency
222900	Sucrose intolerance
223900	Dysautonomia, familial
224100	Congenital dyserythropoietic anemia II
225500	Ellis-van Creveld syndrome
227220	[Eye color, brown]
227646	Fanconi anemia, type D
229300	Friedreich ataxia
229300	Friedreich ataxia with retained reflexes
229600	Fructose intolerance
229800	[Fructosuria]
230000	Fucosidosis
230350	Galactose epimerase deficiency
230400	Galactosemia
230800	Gaucher disease
230800	Gaucher disease with cardiovascular calcification
231550	Achalasia-addisonianism-alacrimia syndrome
231680	Glutaricaciduria, type IIA
232050	Propionicacidemia, type II or pccB type
232200	Glycogen storage disease I
232400	Glycogen storage disease IIIa
232400	Glycogen storage disease IIIb
233100	[Renal glucosuria]
233710	Chronic granulomatous disease due to deficiency of NCF-2
234000	Factor XII deficiency
235200	Hemochromatosis
235800	[Histidinemia]
236100	Holoprosencephaly-1
236200	Homocystinuria, B6-responsive and nonresponsive types
236730	Urofacial syndrome

238310	Hyperglycinemia, nonketotic, type II
239100	Van Buchem disease
240300	Autoimmune polyglandular disease, type I
243500	Isovalericacidemia
245050	Ketoacidosis due to SCOT deficiency
245200	Krabbe disease
245900	Norum disease
245900	Fish-eye disease
246450	HMG-CoA lyase deficiency
246530	Leukotriene C4 synthase deficiency
246900	Lipoamide dehydrogenase deficiency
247200	Miller-Dieker lissencephaly syndrome
248510	Mannosidosis, beta-
248600	Maple syrup urine disease, type Ia
248611	Maple syrup urine disease, type Ib
249000	Meckel syndrome
250100	Metachromatic leukodystrophy
250250	Cartilage-hair hypoplasia
250800	Methemoglobinemia, type I
250800	Methemoglobinemia, type II
251000	Methylmalonicaciduria, mutase deficiency type
251600	Microphthalmia, autosomal recessive
252920	Sanfilippo syndrome, type B
252940	Sanfilippo syndrome, type D
253200	Maroteaux-Lamy syndrome, several forms
253250	Mulibrey nanism
253700	Muscular dystrophy, limb-girdle, type 2C
253800	Walker-Warburg syndrome, 236670
253800	Fukuyama type congenital muscular dystrophy
254210	Myasthenia gravis, familial infantile
255800	Schwartz-Jampel syndrome
256100	Nephronophthisis, juvenile
256540	Galactosialidosis
256550	Sialidosis, type I
256550	Sialidosis, type II
257200	Niemann-Pick disease, type A
257200	Niemann-Pick disease, type B
258501	3-methylglutaconicaciduria, type III
258870	Gyrate atrophy of choroid and retina with ornithinemia, B6 responsive or unresponsive
261510	Pseudo-Zellweger syndrome
261600	Phenylketonuria
261600	[Hyperphenylalaninemia, mild]
261640	Phenylketonuria due to PTS deficiency
263200	Polycystic kidney disease, autosomal recessive
263700	Porphyria, congenital erythropoietic

264300	Pseudohermaphroditism, male, with gynecomastia
264700	Pseudo-vitamin D dependency rickets 1
266200	Anemia, hemolytic, due to PK deficiency
266600	Inflammatory bowel disease-1
267750	Knobloch syndrome
268800	Sandhoff disease, infantile, juvenile, and adult forms
268800	Spinal muscular atrophy, HEXB-related
269920	Salla disease
270100	Situs inversus viscerum
271245	Spinocerebellar ataxia-8, infantile, with sensory neuropathy
271900	Canavan disease
272750	GM2-gangliosidosis, AB variant
272800	Tay-Sachs disease
272800	[Hex A pseudodeficiency]
272800	GM2-gangliosidosis, juvenile, adult
273300	Male germ cell tumor
274600	Pendred syndrome
274600	Deafness, autosomal recessive 4
276600	Tyrosinemia, type II
276700	Tyrosinemia, type I
276900	Usher syndrome, type 1A
276902	Usher syndrome, type 3
278000	Wolman disease
278000	Cholesteryl ester storage disease
278300	Xanthinuria, type I
278760	Xeroderma pigmentosum, group F
300031	Mental retardation, X-linked, FRAXF type
300044	Wernicke-Korsakoff syndrome, susceptibility to
300048	Intestinal pseudoobstruction, neuronal, X-linked
300049	Nodular heterotopia, bilateral periventricular
300049	BPNH/MR syndrome
300055	Mental retardation with psychosis, pyramidal signs, and macroorchidism
300100	Adrenoleukodystrophy
300100	Adrenomyeloneuropathy
300104	Mental retardation, X-linked nonspecific, 309541
300126	Dyskeratosis congenita-1, 305000
301201	Amelogenesis imperfecta-3, hypoplastic type
301220	Partington syndrome II
301590	Anophthalmos-1
302060	Noncompaction of left ventricular myocardium, isolated
302060	Barth syndrome
302060	Cardiomyopathy, X-linked dilated, 300069
302060	Endocardial fibroelastosis-2
302350	Nance-Horan syndrome
302960	Chondrodysplasia punctata, X-linked dominant

303700	Colorblindness, blue monochromatic
303800	Colorblindness, deutan
303900	Colorblindness, protan
304040	Charcot-Marie-Tooth neuropathy, X-linked-1, dominant, 302800
304800	Diabetes insipidus, nephrogenic
305100	Anhidrotic ectodermal dysplasia
305450	FG syndrome
305900	Favism
305900	G6PD deficiency
305900	Hemolytic anemia due to G6PD deficiency
306400	Chronic granulomatous disease, X-linked
306700	Hemophilia A
306995	[Homosexuality, male]
308310	Incontinentia pigmenti, familial
308840	Spastic paraplegia, 312900
308840	Hydrocephalus due to aqueductal stenosis, 307000
308840	MASA syndrome, 303350
309200	Manic-depressive illness, X-linked
309470	Mental retardation, X-linked, syndromic-3, with spastic diplegia
309548	Mental retardation, X-linked, FRAXE type
309585	Mental retardation, X-linked, syndromic-6, with gynecomastia and obesity
309600	Allan-Herndon syndrome
309605	Mental retardation, X-linked, syndromic-4, with congenital contractures and low fingertip arches
309620	Mental retardation-skeletal dysplasia
309900	Mucopolysaccharidosis II
310300	Emery-Dreifuss muscular dystrophy
310400	Myotubular myopathy, X-linked
310460	Myopia-1
310460	Bornholm eye disease
311250	Ornithine transcarbamylase deficiency
311300	Otopalatodigital syndrome, type I
311360	Ovarian failure, premature
311510	Waisman parkinsonism-mental retardation syndrome
312040	N syndrome, 310465
312610	Retinitis pigmentosa-3
312760	Turner syndrome
314250	Dystonia-3, torsion, with parkinsonism, Filipino type
314300	Goeminne TKCR syndrome
314400	Cardiac valvular dysplasia-1
314580	Wieacker-Wolff syndrome
314850	McLeod phenotype
400003	Sertoli-cell-only syndrome
415000	Sertoli-cell-only syndrome
600020	Prostate cancer, 176807

600040	Colorectal cancer
600049	Myelodysplasia syndrome-1
600059	Retinitis pigmentosa-13
600065	Leukocyte adhesion deficiency, 116920
600095	Split hand/foot malformation, type 3
600101	Deafness, autosomal dominant 2
600105	Retinitis pigmentosa-12, autosomal recessive
600119	Muscular dystrophy, Duchenne-like, type 2
600119	Adhalinopathy, primary
600138	Retinitis pigmentosa-11
600163	Long QT syndrome-3
600173	SCID, autosomal recessive, T-negative/B-positive type
600175	Spinal muscular atrophy, congenital nonprogressive, of lower limbs
600179	Leber congenital amaurosis, type I, 204000
600184	Carnitine acetyltransferase deficiency
600194	Ichthyosis bullosa of Siemens, 146800
600202	Dyslexia, specific, 2
600211	Cleidocranial dysplasia, 119600
600223	Spinocerebellar ataxia-4
600231	Palmoplantar keratoderma, Bothnia type
600243	Temperature-sensitive apoptosis
600261	Ehlers-Danlos-like syndrome
600276	Cerebral arteriopathy with subcortical infarcts and leukoencephalopathy, 125310
600281	Non-insulin-dependent diabetes mellitus, 125853
600281	MODY, type 1, 125850
600309	Atrioventricular canal defect-1
600310	Pseudoachondroplasia, 177170
600310	Epiphyseal dysplasia, multiple 1, 132400
600320	Insulin-dependent diabetes mellitus-5
600334	Tibial muscular dystrophy
600354	Spinal muscular atrophy-1, 253300
600354	Spinal muscular atrophy-2, 253550
600354	Spinal muscular atrophy-3, 253400
600374	Bardet-Biedl syndrome 4
600429	[Ii blood group, 110800]
600512	Epilepsy, partial
600536	Myopathy, congenital
600542	Chondrosarcoma, extraskeletal myxoid
600584	Atrial septal defect with atrioventricular conduction defects, 108900
600593	Craniosynostosis, Adelaide type
600650	Myopathy due to CPT II deficiency, 255110
600650	CPT deficiency, hepatic, type II, 600649
600652	Deafness, autosomal dominant 4

600698	Salivary adenoma
600698	Uterine leiomyoma
600698	Lipoma
600698	Lipomatosis, mutiple, 151900
600701	Lipoma
600722	Ceroid lipofuscinosis, neuronal, variant juvenile type, with granular osmiophilic deposits
600722	Ceroid lipofuscinosis, neuronal-1, infantile, 256730
600757	Orofacial cleft-3
600759	Alzheimer disease-4
600760	Pseudohypoaldosteronism, type I, 264350
600760	Liddle syndrome, 177200
600761	Pseudohypoaldosteronism, type I, 264350
600761	Liddle syndrome, 177200
600807	Bronchial asthma
600808	Enuresis, nocturnal, 2
600837	Hirschsprung disease, 142623
600839	Bartter syndrome, 241200
600850	Schizophrenia disorder-4
600856	Beckwith-Wiedemann syndrome, 130650
600881	Cataract, congenital, zonular, with sutural opacities
600882	Charcot-Marie-Tooth neuropathy-2B
600883	Diabetes mellitus, insulin-dependent, 8
600884	Cardiomyopathy, familial dilated 1B
600887	Endometrial carcinoma
600897	Cataract, zonular pulverulent-1, 116200
600899	Severe combined immunodeficiency, type I, 202500
600918	Cystinuria, type III
600919	Long QT syndrome-4 with sinus bradycardia
600923	Porphyria variegata, 176200
600946	Short stature, autosomal dominant, with normal serum growth hormone binding protein
600946	Short stature, idiopathic
600946	Laron dwarfism, 262500
600956	Persistent Mullerian duct syndrome, type II, 261550
600957	Persistent Mullerian duct syndrome, type I, 261550
600968	Gitelman syndrome, 263800
600971	Deafness, autosomal recessive 6
600974	Deafness, autosomal recessive 7
600977	Cone dystrophy, progressive
600994	Deafness, autosomal dominant 5
600995	Nephrotic syndrome, idiopathic, steroid-resistant
600998	Bleeding diathesis due to GNAQ deficiency
601002	5-oxoprolinuria, 266130
601002	Hemolytic anemia due to glutathione synthetase deficiency, 231900

601071	Deafness, autosomal recessive 9
601072	Deafness, autosomal recessive 8
601105	Pycnodysostosis, 265800
601107	Dubin-Johnson syndrome, 237500
601130	Tolbutamide poor metabolizer
601145	Epilepsy, progressive myoclonic 1, 254800
601146	Brachydactyly, type C, 113100
601146	Acromesomelic dysplasia, Hunter-Thompson type, 201250
601146	Chondrodysplasia, Grebe type, 200700
601154	Cardiomyopathy, dilated, 1E
601199	Neonatal hyperparathyroidism, 239200
601199	Hypocalcemia, autosomal dominant, 601198
601199	Hypocalciuric hypercalcemia, type I, 145980
601202	Cataract, anterior polar-2
601208	Insulin-dependent diabetes mellitus-11
601226	Progressive external ophthalmoplegia, type 2
601238	Cerebellar ataxia, Cayman type
601267	HIV infection, susceptibility/resistence to
601284	Hereditary hemorrhagic telangiectasia-2, 600376
601313	Polycystic kidney disease, adult type I, 173900
601316	Deafness, autosomal dominant 10
601363	Wilms tumor, type 4
601373	HIV infection, susceptibility/resistance to
601402	Leukemia, myeloid, acute
601406	B-cell non-Hodgkin lymphoma, high-grade
601410	Diabetes mellitus, transient neonatal
601411	Muscular dystrophy, limb-girdle, type 2F, 601287
601412	Deafness, autosomal dominant 7
601414	Retinitis pigmentosa-18
601471	Moebius syndrome-2
601493	Cardiomyopathy, dilated 1C
601494	Cardiomyopathy, familial, dilated-2
601518	Prostate cancer, hereditary, 1, 176807
601542	Rieger syndrome, type 1, 180500
601545	Lissencephaly-1
601596	Charcot-Marie-Tooth neuropathy, demyelinating
601604	Mycobacterial and salmonella infections, susceptibility to
601607	Rhabdoid tumors
601620	Holt-Oram syndrome, 142900
601621	Ulnar-mammary syndrome, 181450
601649	Blepharophimosis, epicanthus inversus, and ptosis, type 2
601652	Glaucoma 1A, primary open angle, juvenile-onset, 137750
601669	Hirschsprung disease, one form
601680	Distal arthrogryposis, type 2B
601682	Glaucoma 1C, primary open angle
601690	Platelet-activating factor acetylhydrolase deficiency

601691	Retinitis pigmentosa-19, 601718
601691	Stargardt disease-1, 248200
601691	Cone-rod dystrophy 3
601691	Fundus flavimaculatus with macular dystrophy, 248200
601718	Retinitis pigmentosa-19
601757	Rhizomelic chondrodysplasia punctata, type 1, 215100
601769	Osteoporosis, involutional
601769	Rickets, vitamin D-resistant, 277440
601771	Glaucoma 3A, primary infantile, 231300
601777	Cone dystrophy, progressive
601780	Ceroid-lipofuscinosis, neuronal-6, variant late infantile
601800	[Hair color, brown]
601841	Protein C inhibitor deficiency
601843	Hypothyroidism, congenital, 274400
601844	Pseudohypoaldosteronism type II
601846	Muscular dystrophy with rimmed vacuoles
601863	Bare lymphocyte syndrome, complementation group C
601868	Deafness, autosomal dominant 13
601885	Cataract, zonular pulverulent-2
601916	Pancreatic cancer
601928	Monilethrix, 158000
601954	Muscular dystrophy, limb-girdle, type 2G
601969	Glioblastoma multiforme, 137800
601969	Medulloblastoma, 155255
601975	Ectodermal dysplasia/skin fragility syndrome
602014	Hypomagnesemia with secondary hypocalcemia
602066	Convulsions, infantile and paroxysmal choreoathetosis
602067	Cardiomyopathy, dilated, 1F
602081	Speech-language disorder-1
602082	Corneal dystrophy, Thiel-Behnke type
602084	Endometrial carcinoma
602088	Nephronophthisis, infantile
602089	Hemangioma, capillary, hereditary
602092	Deafness, autosomal recessive 18
602094	Lipodystrophy, familial partial
602116	Glioma
602134	Tremor, familial essential, 2
602136	Refsum disease, infantile, 266510
602136	Zellweger syndrome-1, 214100
602136	Adrenoleukodystrophy, neonatal, 202370
602153	Monilethrix, 158000
602216	Peutz-Jeghers syndrome, 175200
602221	Stem-cell leukemia/lymphoma syndrome
602225	Cone-rod retinal dystrophy-2, 120970
602225	Leber congenital amaurosis, type III
602279	Oculopharyngeal muscular dystorphy, 164300

602279	Oculopharyngeal muscular dystrophy, autosomal recessive, 257950
602280	Retinitis pigmentosa-14, 600132
602363	Ellis-van Creveld-like syndrome
602403	Alzheimer disease, susceptibility to
602421	Sweat chloride elevation without CF
602421	Congenital bilateral absence of vas deferens, 277180
602421	Cystic fibrosis, 219700
602447	Coronary artery disease, susceptibility to
602475	Ossification of posterior longitudinal ligament of spine
602476	Febrile convulsions, familial, 1
602477	Febrile convulsions, familial, 2
602491	Hyperlipidemia, familial combined, 1
602544	Parkinson disease, juvenile, type 2, 600116
602568	Homocystinuria-megaloblastic anemia, cbl E type, 236270
602574	Deafness, autosomal dominant 12, 601842
602574	Deafness, autosomal dominant 8, 601543
602575	Nail-patella syndrome with open-angle glaucoma, 137750
602575	Nail-patella syndrome, 161200
602629	Dystonia-6, torsion
602631	Rhabdomyosarcoma, 268210
602631	Breast Cancer
602669	Anterior segment mesenchymal dysgenesis and cataract, 107250
602669	Cataract, congenital
602685	Mental retardation, severe, with spasticity and tapetoretinal degeneration
602716	Nephrosis-1, congenital, Finnish type, 256300
602771	Muscular dystrophy, congenital, with early spine rigidity
602772	Retinitis pitmentosa-24

Polynucleotide and Polypeptide Variants

[091] The present invention is also directed to variants of the immune/hematopoietic associated polynucleotide sequence disclosed in SEQ ID NO:X or the complementary strand thereto, nucleotide sequences encoding the polypeptide of SEQ ID NO:Y, the nucleotide sequence of SEQ ID NO:X encoding the polypeptide sequence as defined in column 6 of Table 1A, nucleotide sequences encoding the polypeptide as defined in column 6 of Table 1A, the nucleotide sequence as defined in columns 8 and 9 of Table 2, nucleotide sequences encoding the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2, the nucleotide sequence as defined in column 6 of Table 1B, nucleotide sequences encoding the polypeptide encoded by the nucleotide sequence as defined in column 6 of Table 1B, the cDNA sequence contained in Clone ID NO:Z, and/or nucleotide sequences encoding a polypeptide encoded by the cDNA sequence contained in Clone ID NO:Z.

[092] The present invention also encompasses variants of the polypeptide sequence disclosed in SEQ ID NO:Y, a polypeptide sequence as defined in column 6 of Table 1A, a polypeptide sequence encoded by the polynucleotide sequence in SEQ ID NO:X, a polypeptide sequence encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2, a polypeptide sequence encoded by the nucleotide sequence as defined in column 6 of Table 1B, a polypeptide sequence encoded by the complement of the polynucleotide sequence in SEQ ID NO:X, and/or a polypeptide sequence encoded by the cDNA sequence contained in Clone ID NO:Z.

[093] "Variant" refers to a polynucleotide or polypeptide differing from the polynucleotide or polypeptide of the present invention, but retaining essential properties thereof. Generally, variants are overall closely similar, and, in many regions, identical to the polynucleotide or polypeptide of the present invention.

[094] Thus, one aspect of the invention provides an isolated nucleic acid molecule comprising, or alternatively consisting of, a polynucleotide having a nucleotide sequence selected from the group consisting of: (a) a nucleotide sequence described in SEQ ID NO:X or contained in the cDNA sequence of Clone ID NO:Z; (b) a nucleotide sequence in SEQ ID NO:X or the cDNA in Clone ID NO:Z which encodes a mature immune/hematopoietic associated polypeptide; (c) a nucleotide sequence in SEQ ID NO:X or the cDNA sequence of Clone ID NO:Z, which encodes a biologically active

fragment of an immune/hematopoietic associated polypeptide; (d) a nucleotide sequence in SEQ ID NO:X or the cDNA sequence of Clone ID NO:Z, which encodes an antigenic fragment of an immune/hematopoietic associated polypeptide; (e) a nucleotide sequence encoding an immune/hematopoietic associated polypeptide having the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in Clone ID NO:Z; (f) a nucleotide sequence encoding a mature immune/hematopoietic associated polypeptide of the amino acid sequence of SEQ ID NO:Y or the amino acid sequence encoded by the cDNA in Clone ID NO:Z; (g) a nucleotide sequence encoding a biologically active fragment of an immune/hematopoietic associated polypeptide having the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in Clone ID NO:Z; (h) a nucleotide sequence encoding an antigenic fragment of an immune/hematopoietic associated polypeptide having the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in Clone ID NO:Z; and (i) a nucleotide sequence complementary to any of the nucleotide sequences in (a), (b), (c), (d), (e), (f), (g), or (h), above.

[095] The present invention is also directed to nucleic acid molecules which comprise, or alternatively consist of, a nucleotide sequence which is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100%, identical to, for example, any of the nucleotide sequences in (a), (b), (c), (d), (e), (f), (g), (h), or (i) above, the nucleotide coding sequence in SEQ ID NO:X or the complementary strand thereto, the nucleotide coding sequence of the cDNA contained in Clone ID NO:Z or the complementary strand thereto, a nucleotide sequence encoding the polypeptide of SEQ ID NO:Y, a nucleotide sequence encoding a polypeptide sequence encoded by the nucleotide sequence in SEQ ID NO:X, a polypeptide sequence encoded by the complement of the polynucleotide sequence in SEQ ID NO:X, a nucleotide sequence encoding the polypeptide encoded by the cDNA contained in Clone ID NO:Z, the nucleotide coding sequence in SEQ ID NO:X as defined in columns 8 and 9 of Table 2 or the complementary strand thereto, a nucleotide sequence encoding the polypeptide encoded by the nucleotide sequence in SEQ ID NO:X as defined in columns 8 and 9 of Table 2 or the complementary strand thereto, the nucleotide coding sequence in SEQ ID NO:B as defined in column 6 of Table 1B or the complementary strand thereto, a nucleotide sequence encoding the polypeptide encoded by the nucleotide sequence in SEQ

ID NO:B as defined in column 6 of Table 1B or the complementary strand thereto, the nucleotide sequence in SEQ ID NO:X encoding the polypeptide sequence as defined in column 6 of Table 1A or the complementary strand thereto, nucleotide sequences encoding a polypeptide as defined in column 6 of Table 1A or the complementary strand thereto, and/or polynucleotide fragments of any of these nucleic acid molecules (e.g., those fragments described herein). Polynucleotides which hybridize to the complement of these nucleic acid molecules under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention, as are polypeptides encoded by these polynucleotides and nucleic acids.

[096] In a preferred embodiment, the invention encompasses nucleic acid molecules which comprise, or alternatively, consist of a polynucleotide which hybridizes under stringent hybridization conditions, or alternatively, under lower stringency conditions, to a polynucleotide in (a), (b), (c), (d), (e), (f), (g), (h), or (i) above, as are polypeptides encoded by these polynucleotides. In another preferred embodiment, polynucleotides which hybridize to the complement of these nucleic acid molecules under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention, as are polypeptides encoded by these polynucleotides.

[097] In another embodiment, the invention provides a purified protein comprising, or alternatively consisting of, a polypeptide having an amino acid sequence selected from the group consisting of: (a) the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in Clone ID NO:Z; (b) the amino acid sequence of a mature immune/hematopoietic associated polypeptide having the amino acid sequence of SEQ ID NO:Y or the amino acid sequence encoded by the cDNA in Clone ID NO:Z; (c) the amino acid sequence of a biologically active fragment of an immune/hematopoietic associated polypeptide having the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in Clone ID NO:Z; and (d) the amino acid sequence of an antigenic fragment of an immune/hematopoietic associated polypeptide having the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in Clone ID NO:Z.

[098] The present invention is also directed to proteins which comprise, or alternatively consist of, an amino acid sequence which is at least 80%, 85%, 90%, 95%,

96%, 97%, 98%, 99% or 100%, identical to, for example, any of the amino acid sequences in (a), (b), (c), or (d), above, the amino acid sequence shown in SEQ ID NO:Y, the amino acid sequence encoded by the cDNA contained in Clone ID NO:Z, the amino acid sequence of the polypeptide encoded by the nucleotide sequence in SEQ ID NO:X as defined in columns 8 and 9 of Table 2, the amino acid sequence of the polypeptide encoded by the nucleotide sequence in SEQ ID NO:B as defined in column 6 of Table 1B, the amino acid sequence as defined in column 6 of Table 1A, an amino acid sequence encoded by the nucleotide sequence in SEQ ID NO:X, and an amino acid sequence encoded by the complement of the polynucleotide sequence in SEQ ID NO:X. Fragments of these polypeptides are also provided (e.g., those fragments described herein). Further proteins encoded by polynucleotides which hybridize to the complement of the nucleic acid molecules encoding these amino acid sequences under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention, as are the polynucleotides encoding these proteins.

[099] By a nucleic acid having a nucleotide sequence at least, for example, 95% "identical" to a reference nucleotide sequence of the present invention, it is intended that the nucleotide sequence of the nucleic acid is identical to the reference sequence except that the nucleotide sequence may include up to five point mutations per each 100 nucleotides of the reference nucleotide sequence encoding the polypeptide. In other words, to obtain a nucleic acid having a nucleotide sequence at least 95% identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence may be deleted or substituted with another nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence may be inserted into the reference sequence. The query sequence may be an entire sequence referred to in Table 1A or 2 as the ORF (open reading frame), or any fragment specified, as described herein.

[0100] As a practical matter, whether any particular nucleic acid molecule or polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to a nucleotide sequence of the present invention can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. 6:237-245

(1990)). In a sequence alignment the query and subject sequences are both DNA sequences. An RNA sequence can be compared by converting U's to T's. The result of said global sequence alignment is expressed as percent identity. Preferred parameters used in a FASTDB alignment of DNA sequences to calculate percent identity are: Matrix=Unitary, k-tuple=4, Mismatch Penalty=1, Joining Penalty=30, Randomization Group Length=0, Cutoff Score=1, Gap Penalty=5, Gap Size Penalty 0.05, Window Size=500 or the length of the subject nucleotide sequence, whichever is shorter.

[0101] If the subject sequence is shorter than the query sequence because of 5' or 3' deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for 5' and 3' truncations of the subject sequence when calculating percent identity. For subject sequences truncated at the 5' or 3' ends, relative to the query sequence, the percent identity is corrected by calculating the number of bases of the query sequence that are 5' and 3' of the subject sequence, which are not matched/aligned, as a percent of the total bases of the query sequence. Whether a nucleotide is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This corrected score is what is used for the purposes of the present invention. Only bases outside the 5' and 3' bases of the subject sequence, as displayed by the FASTDB alignment, which are not matched/aligned with the query sequence, are calculated for the purposes of manually adjusting the percent identity score.

[0102] For example, a 90 base subject sequence is aligned to a 100 base query sequence to determine percent identity. The deletions occur at the 5' end of the subject sequence and therefore, the FASTDB alignment does not show a matched/alignment of the first 10 bases at 5' end. The 10 unpaired bases represent 10% of the sequence (number of bases at the 5' and 3' ends not matched/total number of bases in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 bases were perfectly matched the final percent identity would be 90%. In another example, a 90 base subject sequence is compared with a 100 base query sequence. This time the deletions are internal deletions so that there are no bases on the 5' or 3' of the subject sequence which are not matched/aligned with the query. In this case

the percent identity calculated by FASTDB is not manually corrected. Once again, only bases 5' and 3' of the subject sequence which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to be made for the purposes of the present invention.

[0103] By a polypeptide having an amino acid sequence at least, for example, 95% "identical" to a query amino acid sequence of the present invention, it is intended that the amino acid sequence of the subject polypeptide is identical to the query sequence except that the subject polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the query amino acid sequence. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a query amino acid sequence, up to 5% of the amino acid residues in the subject sequence may be inserted, deleted, (indels) or substituted with another amino acid. These alterations of the reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

[0104] As a practical matter, whether any particular polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequence of a polypeptide referred to in Table 1A (e.g., an amino acid sequence identified in columns 5 or 6) or Table 2 (e.g., the amino acid sequence of the polypeptide encoded by the polynucleotide sequence defined in columns 8 and 9 of Table 2) or a fragment thereof, the amino acid sequence of the polypeptide encoded by the polynucleotide sequence in SEQ ID NO:B as defined in column 6 of Table 1B or a fragment thereof, the amino acid sequence of the polypeptide encoded by the nucleotide sequence in SEQ ID NO:X or a fragment thereof, or an amino acid sequence of the polypeptide encoded by cDNA contained in Clone ID NO:Z, or a fragment thereof, can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci.6:237-245 (1990)). In a sequence alignment the query and subject sequences are either both nucleotide sequences or both amino acid sequences. The result of said global

sequence alignment is expressed as percent identity. Preferred parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject amino acid sequence, whichever is shorter.

[0105] If the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global percent identity. For subject sequences truncated at the N- and C-termini, relative to the query sequence, the percent identity is corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject residue, as a percent of the total bases of the query sequence. Whether a residue is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of the present invention. Only residues to the N- and C-termini of the subject sequence, which are not matched/aligned with the query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C- terminal residues of the subject sequence.

[0106] For example, a 90 amino acid residue subject sequence is aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C- termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence. This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent

identity calculated by FASTDB is not manually corrected. Once again, only residue positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to be made for the purposes of the present invention.

[0107] The polynucleotide variants of the invention may contain alterations in the coding regions, non-coding regions, or both. Especially preferred are polynucleotide variants containing alterations which produce silent substitutions, additions, or deletions, but do not alter the properties or activities of the encoded polypeptide. Nucleotide variants produced by silent substitutions due to the degeneracy of the genetic code are preferred. Moreover, polypeptide variants in which less than 50, less than 40, less than 30, less than 20, less than 10, or 5-50, 5-25, 5-10, 1-5, or 1-2 amino acids are substituted, deleted, or added in any combination are also preferred. Polynucleotide variants can be produced for a variety of reasons, e.g., to optimize codon expression for a particular host (change codons in the human mRNA to those preferred by a bacterial host such as *E. coli*).

[0108] Naturally occurring variants are called "allelic variants," and refer to one of several alternate forms of a gene occupying a given locus on a chromosome of an organism. (Genes II, Lewin, B., ed., John Wiley & Sons, New York (1985).) These allelic variants can vary at either the polynucleotide and/or polypeptide level and are included in the present invention. Alternatively, non-naturally occurring variants may be produced by mutagenesis techniques or by direct synthesis.

[0109] Using known methods of protein engineering and recombinant DNA technology, variants may be generated to improve or alter the characteristics of the polypeptides of the present invention. For instance, one or more amino acids can be deleted from the N-terminus or C-terminus of the polypeptides of the present invention without substantial loss of biological function. As an example, the authors of Ron et al., J. Biol. Chem. 268: 2984-2988 (1993), reported variant KGF proteins having heparin binding activity even after deleting 3, 8, or 27 amino-terminal amino acid residues. Similarly, Interferon gamma exhibited up to ten times higher activity after deleting 8-10 amino acid residues from the carboxy terminus of this protein. (Dobeli et al., J. Biotechnology 7:199-216 (1988).)

[0110] Moreover, ample evidence demonstrates that variants often retain a biological activity similar to that of the naturally occurring protein. For example, Gayle and coworkers (J. Biol. Chem. 268:22105-22111 (1993)) conducted extensive mutational analysis of human cytokine IL-1a. They used random mutagenesis to generate over 3,500 individual IL-1a mutants that averaged 2.5 amino acid changes per variant over the entire length of the molecule. Multiple mutations were examined at every possible amino acid position. The investigators found that "[m]ost of the molecule could be altered with little effect on either [binding or biological activity]." In fact, only 23 unique amino acid sequences, out of more than 3,500 nucleotide sequences examined, produced a protein that significantly differed in activity from wild-type.

[0111] Furthermore, even if deleting one or more amino acids from the N-terminus or C-terminus of a polypeptide results in modification or loss of one or more biological functions, other biological activities may still be retained. For example, the ability of a deletion variant to induce and/or to bind antibodies which recognize the secreted form will likely be retained when less than the majority of the residues of the secreted form are removed from the N-terminus or C-terminus. Whether a particular polypeptide lacking N- or C-terminal residues of a protein retains such immunogenic activities can readily be determined by routine methods described herein and otherwise known in the art.

[0112] Thus, the invention further includes polypeptide variants which show a functional activity (e.g., biological activity) of the polypeptides of the invention. Such variants include deletions, insertions, inversions, repeats, and substitutions selected according to general rules known in the art so as have little effect on activity.

[0113] The present application is directed to nucleic acid molecules at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleic acid sequences disclosed herein, (e.g., encoding a polypeptide having the amino acid sequence of an N and/or C terminal deletion), irrespective of whether they encode a polypeptide having functional activity. This is because even where a particular nucleic acid molecule does not encode a polypeptide having functional activity, one of skill in the art would still know how to use the nucleic acid molecule, for instance, as a hybridization probe or a polymerase chain reaction (PCR) primer. Uses of the nucleic acid molecules of the present invention that do not encode a polypeptide having functional activity include, *inter alia*, (1) isolating a gene or allelic or splice variants thereof in a cDNA library; (2) in situ

hybridization (e.g., "FISH") to metaphase chromosomal spreads to provide precise chromosomal location of the gene, as described in Verma et al., Human Chromosomes: A Manual of Basic Techniques, Pergamon Press, New York (1988); (3) Northern Blot analysis for detecting mRNA expression in specific tissues (e.g., normal immune/hematopoietic or diseased immune/hematopoietic tissues); and (4) *in situ* hybridization (e.g., histochemistry) for detecting mRNA expression in specific tissues (e.g., normal immune/hematopoietic or diseased immune/hematopoietic tissues).

[0114] Preferred, however, are nucleic acid molecules having sequences at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleic acid sequences disclosed herein, which do, in fact, encode a polypeptide having functional activity. By a polypeptide having "functional activity" is meant, a polypeptide capable of displaying one or more known functional activities associated with a full-length (complete) protein of the invention. Such functional activities include, but are not limited to, biological activity, antigenicity [ability to bind (or compete with a polypeptide of the invention for binding) to an anti-polypeptide of the invention antibody], immunogenicity (ability to generate antibody which binds to a specific polypeptide of the invention), ability to form multimers with polypeptides of the invention, and ability to bind to a receptor or ligand for a polypeptide of the invention.

[0115] The functional activity of the polypeptides, and fragments, variants and derivatives of the invention, can be assayed by various methods.

[0116] For example, in one embodiment where one is assaying for the ability to bind or compete with full-length polypeptide of the present invention for binding to an anti-polypeptide of the invention antibody, various immunoassays known in the art can be used, including but not limited to, competitive and non-competitive assay systems using techniques such as radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoradiometric assays, gel diffusion precipitation reactions, immunodiffusion assays, in situ immunoassays (using colloidal gold, enzyme or radioisotope labels, for example), western blots, precipitation reactions, agglutination assays (e.g., gel agglutination assays, hemagglutination assays), complement fixation assays, immunofluorescence assays, protein A assays, and immunoelectrophoresis assays, etc. In one embodiment, antibody binding is detected by detecting a label on the primary antibody. In another embodiment, the primary antibody is detected by detecting binding

of a secondary antibody or reagent to the primary antibody. In a further embodiment, the secondary antibody is labeled. Many means are known in the art for detecting binding in an immunoassay and are within the scope of the present invention.

[0117] In another embodiment, where a ligand is identified, or the ability of a polypeptide fragment, variant or derivative of the invention to multimerize is being evaluated, binding can be assayed, e.g., by means well-known in the art, such as, for example, reducing and non-reducing gel chromatography, protein affinity chromatography, and affinity blotting. See generally, Phizicky et al., Microbiol. Rev. 59:94-123 (1995). In another embodiment, the ability of physiological correlates of a polypeptide of the present invention to bind to a substrate(s) of the polypeptide of the invention can be routinely assayed using techniques known in the art.

[0118] In addition, assays described herein (see Examples) and otherwise known in the art may routinely be applied to measure the ability of polypeptides of the present invention and fragments, variants and derivatives thereof to elicit polypeptide related biological activity (either *in vitro* or *in vivo*). Other methods will be known to the skilled artisan and are within the scope of the invention.

[0119] Of course, due to the degeneracy of the genetic code, one of ordinary skill in the art will immediately recognize that a large number of the nucleic acid molecules having a sequence at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to, for example, the nucleic acid sequence of the cDNA contained in Clone ID NO:Z, a nucleic acid sequence referred to in Table 1A (e.g., SEQ ID NO:X), a nucleic acid sequence disclosed in Table 2 (e.g., the nucleic acid sequence delineated in columns 8 and 9) or fragments thereof, will encode polypeptides "having functional activity." In fact, since degenerate variants of any of these nucleotide sequences all encode the same polypeptide, in many instances, this will be clear to the skilled artisan even without performing the above described comparison assay. It will be further recognized in the art that, for such nucleic acid molecules that are not degenerate variants, a reasonable number will also encode a polypeptide having functional activity. This is because the skilled artisan is fully aware of amino acid substitutions that are either less likely or not likely to significantly effect protein function (e.g., replacing one aliphatic amino acid with a second aliphatic amino acid), as further described below.

[0120] For example, guidance concerning how to make phenotypically silent amino acid substitutions is provided in Bowie et al., "Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions," Science 247:1306-1310 (1990), wherein the authors indicate that there are two main strategies for studying the tolerance of an amino acid sequence to change.

[0121] The first strategy exploits the tolerance of amino acid substitutions by natural selection during the process of evolution. By comparing amino acid sequences in different species, conserved amino acids can be identified. These conserved amino acids are likely important for protein function. In contrast, the amino acid positions where substitutions have been tolerated by natural selection indicates that these positions are not critical for protein function. Thus, positions tolerating amino acid substitution could be modified while still maintaining biological activity of the protein.

[0122] The second strategy uses genetic engineering to introduce amino acid changes at specific positions of a cloned gene to identify regions critical for protein function. For example, site directed mutagenesis or alanine-scanning mutagenesis (introduction of single alanine mutations at every residue in the molecule) can be used. See Cunningham et al., Science 244:1081-1085 (1989). The resulting mutant molecules can then be tested for biological activity.

[0123] As the authors state, these two strategies have revealed that proteins are surprisingly tolerant of amino acid substitutions. The authors further indicate which amino acid changes are likely to be permissive at certain amino acid positions in the protein. For example, most buried (within the tertiary structure of the protein) amino acid residues require nonpolar side chains, whereas few features of surface side chains are generally conserved. Moreover, tolerated conservative amino acid substitutions involve replacement of the aliphatic or hydrophobic amino acids Ala, Val, Leu and Ile; replacement of the hydroxyl residues Ser and Thr; replacement of the acidic residues Asp and Glu; replacement of the amide residues Asn and Gln, replacement of the basic residues Lys, Arg, and His; replacement of the aromatic residues Phe, Tyr, and Trp, and replacement of the small-sized amino acids Ala, Ser, Thr, Met, and Gly. Besides conservative amino acid substitutions, variants of the present invention include (i) substitutions with one or more of the non-conserved amino acid residues, where the substituted amino acid residues may or may not be one encoded by the genetic code, or (ii)

substitutions with one or more of the amino acid residues having a substituent group, or (iii) fusion of the mature polypeptide with another compound, such as a compound to increase the stability and/or solubility of the polypeptide (for example, polyethylene glycol), or (iv) fusion of the polypeptide with additional amino acids, such as, for example, an IgG Fc fusion region peptide, serum albumin (preferably human serum albumin) or a fragment or variant thereof, or leader or secretory sequence, or a sequence facilitating purification. Such variant polypeptides are deemed to be within the scope of those skilled in the art from the teachings herein.

[0124] For example, polypeptide variants containing amino acid substitutions of charged amino acids with other charged or neutral amino acids may produce proteins with improved characteristics, such as less aggregation. Aggregation of pharmaceutical formulations both reduces activity and increases clearance due to the aggregate's immunogenic activity. See Pinckard et al., Clin. Exp. Immunol. 2:331-340 (1967); Robbins et al., Diabetes 36: 838-845 (1987); Cleland et al., Crit. Rev. Therapeutic Drug Carrier Systems 10:307-377 (1993).

[0125] A further embodiment of the invention relates to polypeptides which comprise the amino acid sequence of a polypeptide having an amino acid sequence which contains at least one amino acid substitution, but not more than 50 amino acid substitutions, even more preferably, not more than 40 amino acid substitutions, still more preferably, not more than 30 amino acid substitutions, and still even more preferably, not more than 20 amino acid substitutions from a polypeptide sequence disclosed herein. Of course it is highly preferable for a polypeptide to have an amino acid sequence which comprises the amino acid sequence of a polypeptide of SEQ ID NO:Y, an amino acid sequence encoded by SEQ ID NO:X, an amino acid sequence encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, an amino acid sequence encoded by the complement of SEQ ID NO:X, and/or the amino acid sequence encoded by cDNA contained in Clone ID NO:Z which contains, in order of ever-increasing preference, at least one, but not more than 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acid substitutions.

[0126] In specific embodiments, the polypeptides of the invention comprise, or alternatively, consist of, fragments or variants of a reference amino acid sequence selected from: (a) the amino acid sequence of SEQ ID NO:Y or fragments thereof (e.g., the mature form and/or other fragments described herein); (b) the amino acid sequence encoded by

SEQ ID NO:X or fragments thereof; (c) the amino acid sequence encoded by the complement of SEQ ID NO:X or fragments thereof; (d) the amino acid sequence encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2 or fragments thereof; and (e) the amino acid sequence encoded by cDNA contained in Clone ID NO:Z or fragments thereof; wherein the fragments or variants have 1-5, 5-10, 5-25, 5-50, 10-50 or 50-150, amino acid residue additions, substitutions, and/or deletions when compared to the reference amino acid sequence. In preferred embodiments, the amino acid substitutions are conservative. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Polynucleotide and Polypeptide Fragments

[0127] The present invention is also directed to polynucleotide fragments of the polynucleotides (nucleic acids) of the invention. In the present invention, a "polynucleotide fragment" refers to a polynucleotide having a nucleic acid sequence which, for example: is a portion of the cDNA contained in Clone ID NO:Z or the complementary strand thereto; is a portion of the polynucleotide sequence encoding the polypeptide encoded by the cDNA contained in Clone ID NO:Z or the complementary strand thereto; is a portion of a polynucleotide sequence encoding the amino acid sequence encoded by the region of SEQ ID NO:X as defined in columns 8 and 9 of Table 2 or the complementary strand thereto; is a portion of the polynucleotide sequence of SEQ ID NO:X as defined in columns 8 and 9 of Table 2 or the complementary strand thereto; is a portion of the polynucleotide sequence in SEQ ID NO:X or the complementary strand thereto; is a polynucleotide sequence encoding a portion of the polypeptide of SEQ ID NO:Y; is a polynucleotide sequence encoding a portion of a polypeptide encoded by SEQ ID NO:X; is a polynucleotide sequence encoding a portion of a polypeptide encoded by the complement of the polynucleotide sequence in SEQ ID NO:X; is a portion of a polynucleotide sequence encoding the amino acid sequence encoded by the region of SEQ ID NO:B as defined in column 6 of Table 1B or the complementary strand thereto; or is a portion of the polynucleotide sequence of SEQ ID NO:B as defined in column 6 of Table 1B or the complementary strand thereto.

[0128] The polynucleotide fragments of the invention are preferably at least about 15 nt, and more preferably at least about 20 nt, still more preferably at least about 30 nt, and

even more preferably, at least about 40 nt, at least about 50 nt, at least about 75 nt, or at least about 150 nt in length. A fragment "at least 20 nt in length," for example, is intended to include 20 or more contiguous bases from the cDNA sequence contained in Clone ID NO:Z, or the nucleotide sequence shown in SEQ ID NO:X or the complementary stand thereto. In this context "about" includes the particularly recited value or a value larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. These nucleotide fragments have uses that include, but are not limited to, as diagnostic probes and primers as discussed herein. Of course, larger fragments (e.g., at least 160, 170, 180, 190, 200, 250, 500, 600, 1000, or 2000 nucleotides in length) are also encompassed by the invention.

[0129] Moreover, representative examples of polynucleotide fragments of the invention, comprise, or alternatively consist of, a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 651-700, 701-750, 751-800, 800-850, 851-900, 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-1300, 1301-1350, 1351-1400, 1401-1450, 1451-1500, 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, 2001-2050, 2051-2100, 2101-2150, 2151-2200, 2201-2250, 2251-2300, 2301-2350, 2351-2400, 2401-2450, 2451-2500, 2501-2550, 2551-2600, 2601-2650, 2651-2700, 2701-2750, 2751-2800, 2801-2850, 2851-2900, 2901-2950, 2951-3000, 3001-3050, 3051-3100, 3101-3150, 3151-3200, 3201-3250, 3251-3300, 3301-3350, 3351-3400, 3401-3450, 3451-3500, 3501-3550, 3551-3600, 3601-3650, 3651-3700, 3701-3750, 3751-3800, 3801-3850, 3851-3900, 3901-3950, 3951-4000, 4001-4050, 4051-4100, 4101-4150, 4151-4200, 4201-4250, 4251-4300, 4301-4350, 4351-4400, 4401-4450, 4451-4500, 4501-4550, 4551-4600, 4601-4650, 4651-4700, 4701-4750, 4751-4800, 4801-4850, 4851-4900, 4901-4950, 4951-5000, 5001-5050, 5051-5100, 5101-5150, 5151-5200, 5201-5250, 5251-5300, 5301-5350, 5351-5400, 5401-5450, 5451-5500, 5501-5550, 5551-5600, 5601-5650, 5651-5700, 5701-5750, 5751-5800, 5801-5850, 5851-5900, 5901-5950, 5951-6000, 6001-6050, 6051-6100, 6101-6150, 6151-6200, 6201-6250, 6251-6300, 6301-6350, 6351-6400, 6401-6450, 6451-6500, 6501-6550, 6551-6600, 6601-6650, 6651-6700, 6701-6750, 6751-6800, 6801-6850, 6851-6900, 6901-6950, 6951-7000, 7001-7050, 7051-7100, 7101-7150, 7151-7200, 7201-7250, 7251-7300 or 7301 to the end of SEQ ID NO:X, or the complementary strand thereto. In this context "about" includes

the particularly recited range or a range larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Preferably, these fragments encode a polypeptide which has a functional activity (e.g., biological activity). More preferably, these polynucleotides can be used as probes or primers as discussed herein. Polynucleotides which hybridize to one or more of these polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions are also encompassed by the invention, as are polypeptides encoded by these polynucleotides.

[0130] Further representative examples of polynucleotide fragments of the invention, comprise, or alternatively consist of, a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 651-700, 701-750, 751-800, 800-850, 851-900, 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-1300, 1301-1350, 1351-1400, 1401-1450, 1451-1500, 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, 2001-2050, 2051-2100, 2101-2150, 2151-2200, 2201-2250, 2251-2300, 2301-2350, 2351-2400, 2401-2450, 2451-2500, 2501-2550, 2551-2600, 2601-2650, 2651-2700, 2701-2750, 2751-2800, 2801-2850, 2851-2900, 2901-2950, 2951-3000, 3001-3050, 3051-3100, 3101-3150, 3151-3200, 3201-3250, 3251-3300, 3301-3350, 3351-3400, 3401-3450, 3451-3500, 3501-3550, 3551-3600, 3601-3650, 3651-3700, 3701-3750, 3751-3800, 3801-3850, 3851-3900, 3901-3950, 3951-4000, 4001-4050, 4051-4100, 4101-4150, 4151-4200, 4201-4250, 4251-4300, 4301-4350, 4351-4400, 4401-4450, 4451-4500, 4501-4550, 4551-4600, 4601-4650, 4651-4700, 4701-4750, 4751-4800, 4801-4850, 4851-4900, 4901-4950, 4951-5000, 5001-5050, 5051-5100, 5101-5150, 5151-5200, 5201-5250, 5251-5300, 5301-5350, 5351-5400, 5401-5450, 5451-5500, 5501-5550, 5551-5600, 5601-5650, 5651-5700, 5701-5750, 5751-5800, 5801-5850, 5851-5900, 5901-5950, 5951-6000, 6001-6050, 6051-6100, 6101-6150, 6151-6200, 6201-6250, 6251-6300, 6301-6350, 6351-6400, 6401-6450, 6451-6500, 6501-6550, 6551-6600, 6601-6650, 6651-6700, 6701-6750, 6751-6800, 6801-6850, 6851-6900, 6901-6950, 6951-7000, 7001-7050, 7051-7100, 7101-7150, 7151-7200, 7201-7250, 7251-7300 or 7301 to the end of the cDNA sequence contained in Clone ID NO:Z, or the complementary strand thereto. In this context "about" includes the particularly recited range or a range larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Preferably, these fragments encode a polypeptide which has a functional activity (e.g., biological activity).

More preferably, these polynucleotides can be used as probes or primers as discussed herein. Polynucleotides which hybridize to one or more of these polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions are also encompassed by the invention, as are polypeptides encoded by these polynucleotides.

[0131] Moreover, representative examples of polynucleotide fragments of the invention comprise, or alternatively consist of, a nucleic acid sequence comprising one, two, three, four, five, six, seven, eight, nine, ten, or more of the above described polynucleotide fragments of the invention in combination with a polynucleotide sequence delineated in Table 1B column 6. Additional, representative examples of polynucleotide fragments of the invention comprise, or alternatively consist of, a nucleic acid sequence comprising one, two, three, four, five, six, seven, eight, nine, ten, or more of the above described polynucleotide fragments of the invention in combination with a polynucleotide sequence that is the complementary strand of a sequence delineated in column 6 of Table 1B. In further embodiments, the above-described polynucleotide fragments of the invention comprise, or alternatively consist of, sequences delineated in Table 1B, column 6, and have a nucleic acid sequence which is different from that of the BAC fragment having the sequence disclosed in SEQ ID NO:B (see Table 1B, column 5). In additional embodiments, the above-described polynucleotide fragments of the invention comprise, or alternatively consist of, sequences delineated in Table 1B, column 6, and have a nucleic acid sequence which is different from that published for the BAC clone identified as BAC ID NO:A (see Table 1B, column 4). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated Table 1B, column 6, and have a nucleic acid sequence which is different from that contained in the BAC clone identified as BAC ID NO:A (see Table 1B, column 4). Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides and polypeptides are also encompassed by the invention.

[0132] In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more fragments of the sequences delineated in column 6 of Table 1B, and the polynucleotide sequence of SEQ ID NO:X (e.g., as defined in Table 1B, column 2) or fragments or

variants thereof. Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

[0133] In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more fragments of the sequences delineated in column 6 of Table 1B which correspond to the same Clone ID NO:Z (see Table 1B, column 1), and the polynucleotide sequence of SEQ ID NO:X (e.g., as defined in Table 1A or 1B) or fragments or variants thereof. Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

[0134] In further specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more fragments of the sequences delineated in the same row of column 6 of Table 1B, and the polynucleotide sequence of SEQ ID NO:X (e.g., as defined in Table 1A or 1B) or fragments or variants thereof. Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

[0135] In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1B and the 5' 10 polynucleotides of the sequence of SEQ ID NO:X are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

[0136] In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1B and the 5' 10 polynucleotides of

a fragment or variant of the sequence of SEQ ID NO:X (e.g., as described herein) are directly contiguous Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

[0137] In further specific embodiments, polynucleotides of the invention comprise, or alternatively consist of a polynucleotide sequence in which the 3' 10 polynucleotides of a fragment or variant of the sequence of SEQ ID NO:X and the 5' 10 polynucleotides of the sequence of one of the sequences delineated in column 6 of Table 1B are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

[0138] In specific embodiments, polynucleotides of the invention comprise, or alternatively consist of a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1B and the 5' 10 polynucleotides of another sequence in column 6 are directly contiguous. In preferred embodiments, the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1B is directly contiguous with the 5' 10 polynucleotides of the next sequential exon delineated in Table 1B, column 6. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also

encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

[0139] In the present invention, a "polypeptide fragment" refers to an amino acid sequence which is a portion of that contained in SEQ ID NO:Y, a portion of an amino acid sequence encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, a portion of an amino acid sequence encoded by the polynucleotide sequence of SEQ ID NO:X, a portion of an amino acid sequence encoded by the complement of the polynucleotide sequence in SEQ ID NO:X, and/or a portion of an amino acid sequence encoded by the cDNA contained in Clone ID NO:Z. Protein (polypeptide) fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments of the invention, include, for example, fragments comprising, or alternatively consisting of, from about amino acid number 1-20, 21-40, 41-60, 61-80, 81-100, 102-120, 121-140, 141-160, 161-180, 181-200, 201-220, 221-240, 241-260, 261-280, 281-300, 301-320, 321-340, 341-360, 361-380, 381-400, 401-420, 421-440, 441-460, 461-480, 481-500, 501-520, 521-540, 541-560, 561-580, 581-600, 601-620, 621-640, 641-660, 661-680, 681-700, 701-720, 721-740, 741-760, 761-780, 781-800, 801-820, 821-840, 841-860, 861-880, 881-900, 901-920, 921-940, 941-960, 961-980, 981-1000, 1001-1020, 1021-1040, 1041-1060, 1061-1080, 1081-1100, 1101-1120, 1121-1140, 1141-1160, 1161-1180, 1181-1200, 1201-1220, 1221-1240, 1241-1260, 1261-1280, 1281-1300, 1301-1320, 1321-1340, 1341-1360, 1361-1380, 1381-1400, 1401-1420, 1421-1440, or 1441 to the end of the coding region. In a preferred embodiment, polypeptide fragments of the invention include, for example, fragments comprising, or alternatively consisting of, from about amino acid number 1-20, 21-40, 41-60, 61-80, 81-100, 102-120, 121-140, 141-160, 161-180, 181-200, 201-220, 221-240, 241-260, 261-280, 281-300, 301-320, 321-340, 341-360, 361-380, 381-400, 401-420, 421-440, 441-460, 461-480, 481-500, 501-520, 521-540, 541-560, 561-580, 581-600, 601-620, 621-640, 641-660, 661-680, 681-700, 701-720, 721-740, 741-760, 761-780, 781-800, 801-820, 821-840, 841-860, 861-880, 881-900, 901-920, 921-940, 941-960, 961-980, 981-1000, 1001-1020, 1021-1040, 1041-1060, 1061-1080, 1081-1100, 1101-1120, 1121-1140, 1141-1160, 1161-1180, 1181-1200, 1201-1220, 1221-1240, 1241-1260, 1261-1280, 1281-1300, 1301-1320, 1321-1340, 1341-1360, 1361-1380, 1381-

1400, 1401-1420, 1421-1440, or 1441 to the end of the coding region of SEQ ID NO:Y. Moreover, polypeptide fragments of the invention may be at least about 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 100, 110, 120, 130, 140, or 150 amino acids in length. In this context "about" includes the particularly recited ranges or values, or ranges or values larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes. Polynucleotides encoding these polypeptide fragments are also encompassed by the invention.

[0140] Even if deletion of one or more amino acids from the N-terminus of a protein results in modification of loss of one or more biological functions of the protein, other functional activities (e.g., biological activities, ability to multimerize, ability to bind a ligand) may still be retained. For example, the ability of shortened muteins to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptides generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a mutein with a large number of deleted N-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.

[0141] Accordingly, polypeptide fragments include the secreted protein as well as the mature form. Further preferred polypeptide fragments include the secreted protein or the mature form having a continuous series of deleted residues from the amino or the carboxy terminus, or both. For example, any number of amino acids, ranging from 1-60, can be deleted from the amino terminus of either the secreted polypeptide or the mature form. Similarly, any number of amino acids, ranging from 1-30, can be deleted from the carboxy terminus of the secreted protein or mature form. Furthermore, any combination of the above amino and carboxy terminus deletions is preferred. Similarly, polynucleotides encoding these polypeptide fragments are also preferred.

[0142] The present invention further provides polypeptides having one or more residues deleted from the amino terminus of the amino acid sequence of a polypeptide disclosed herein (e.g., a polypeptide of SEQ ID NO:Y, a polypeptide encoded by the

polynucleotide sequence contained in SEQ ID NO:X or the complement thereof, a polypeptide encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, a polypeptide encoded by the portion of SEQ ID NO:B as defined in column 6 of Table 1B, and/or a polypeptide encoded by the cDNA contained in Clone ID NO:Z). In particular, N-terminal deletions may be described by the general formula m-q, where q is a whole integer representing the total number of amino acid residues in a polypeptide of the invention (e.g., the polypeptide disclosed in SEQ ID NO:Y, or the polypeptide encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2), and m is defined as any integer ranging from 2 to q-6. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0143] The present invention further provides polypeptides having one or more residues from the carboxy terminus of the amino acid sequence of a polypeptide disclosed herein (e.g., a polypeptide of SEQ ID NO:Y, a polypeptide encoded by the polynucleotide sequence contained in SEQ ID NO:X, a polypeptide encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, and/or a polypeptide encoded by the cDNA contained in Clone ID NO:Z). In particular, C-terminal deletions may be described by the general formula 1-n, where n is any whole integer ranging from 6 to q-1, and where n corresponds to the position of amino acid residue in a polypeptide of the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0144] In addition, any of the above described N- or C-terminal deletions can be combined to produce a N- and C-terminal deleted polypeptide. The invention also provides polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini, which may be described generally as having residues m-n of a polypeptide encoded by SEQ ID NO:X (e.g., including, but not limited to, the preferred polypeptide disclosed as SEQ ID NO:Y and the polypeptide encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2), the cDNA contained in Clone ID NO:Z, and/or the complement thereof, where n and m are integers as described above. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0145] Also as mentioned above, even if deletion of one or more amino acids from the C-terminus of a protein results in modification of loss of one or more biological functions of the protein, other functional activities (e.g., biological activities, ability to multimerize, ability to bind a ligand) may still be retained. For example the ability of the shortened

mutein to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptide generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a mutein with a large number of deleted C-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.

[0146] The present application is also directed to proteins containing polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to a polypeptide sequence set forth herein. In preferred embodiments, the application is directed to proteins containing polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to polypeptides having the amino acid sequence of the specific N- and C-terminal deletions. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0147] Any polypeptide sequence encoded by, for example, the polynucleotide sequences set forth as SEQ ID NO:X or the complement thereof, (presented, for example, in Tables 1A and 2), the cDNA contained in Clone ID NO:Z, or the polynucleotide sequence as defined in column 6 of Table 1B, may be analyzed to determine certain preferred regions of the polypeptide. For example, the amino acid sequence of a polypeptide encoded by a polynucleotide sequence of SEQ ID NO:X (e.g., the polypeptide of SEQ ID NO:Y and the polypeptide encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2) or the cDNA contained in Clone ID NO:Z may be analyzed using the default parameters of the DNASTAR computer algorithm (DNASTAR, Inc., 1228 S. Park St., Madison, WI 53715 USA; http://www.dnastar.com/).

[0148] Polypeptide regions that may be routinely obtained using the DNASTAR computer algorithm include, but are not limited to, Garnier-Robson alpha-regions, beta-regions, turn-regions, and coil-regions; Chou-Fasman alpha-regions, beta-regions, and turn-regions; Kyte-Doolittle hydrophilic regions and hydrophobic regions; Eisenberg alpha- and beta-amphipathic regions; Karplus-Schulz flexible regions; Emini surface-forming regions; and Jameson-Wolf regions of high antigenic index. Among

highly preferred polynucleotides of the invention in this regard are those that encode polypeptides comprising regions that combine several structural features, such as several (e.g., 1, 2, 3 or 4) of the features set out above.

[0149] Additionally, Kyte-Doolittle hydrophilic regions and hydrophobic regions, Emini surface-forming regions, and Jameson-Wolf regions of high antigenic index (i.e., containing four or more contiguous amino acids having an antigenic index of greater than or equal to 1.5, as identified using the default parameters of the Jameson-Wolf program) can routinely be used to determine polypeptide regions that exhibit a high degree of potential for antigenicity. Regions of high antigenicity are determined from data by DNASTAR analysis by choosing values which represent regions of the polypeptide which are likely to be exposed on the surface of the polypeptide in an environment in which antigen recognition may occur in the process of initiation of an immune response.

[0150] Preferred polypeptide fragments of the invention are fragments comprising, or alternatively, consisting of, an amino acid sequence that displays a functional activity (e.g. biological activity) of the polypeptide sequence of which the amino acid sequence is a fragment. By a polypeptide displaying a "functional activity" is meant a polypeptide capable of one or more known functional activities associated with a full-length protein, such as, for example, biological activity, antigenicity, immunogenicity, and/or multimerization, as described herein.

[0151] Other preferred polypeptide fragments are biologically active fragments. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

[0152] In preferred embodiments, polypeptides of the invention comprise, or alternatively consist of, one, two, three, four, five or more of the antigenic fragments of the polypeptide of SEQ ID NO:Y, or portions thereof. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0153] The present invention encompasses polypeptides comprising, or alternatively consisting of, an epitope of: the polypeptide sequence shown in SEQ ID NO:Y; a polypeptide sequence encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide sequence encoded by the portion of SEQ ID NO:X as defined in columns 8

and 9 of Table 2; the polypeptide sequence encoded by the portion of SEQ ID NO:B as defined in column 6 of Table 1B or the complement thereto; the polypeptide sequence encoded by the cDNA contained in Clone ID NO:Z; or the polypeptide sequence encoded by a polynucleotide that hybridizes to the sequence of SEQ ID NO:X, the complement of the sequence of SEQ ID NO:X, the complement of a portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, or the cDNA sequence contained in Clone ID NO:Z under stringent hybridization conditions or alternatively, under lower stringency hybridization as defined *supra*. The present invention further encompasses polynucleotide sequences encoding an epitope of a polypeptide sequence of the invention (such as, for example, the sequence disclosed in SEQ ID NO:X, or a fragment thereof), polynucleotide sequences of the complementary strand of a polynucleotide sequence encoding an epitope of the invention, and polynucleotide sequences which hybridize to the complementary strand under stringent hybridization conditions or alternatively, under lower stringency hybridization conditions defined *supra*.

[0154] The term "epitopes," as used herein, refers to portions of a polypeptide having antigenic or immunogenic activity in an animal, preferably a mammal, and most preferably in a human. In a preferred embodiment, the present invention encompasses a polypeptide comprising an epitope, as well as the polynucleotide encoding this polypeptide. An "immunogenic epitope," as used herein, is defined as a portion of a protein that elicits an antibody response in an animal, as determined by any method known in the art, for example, by the methods for generating antibodies described *infra*. (See, for example, Geysen et al., Proc. Natl. Acad. Sci. USA 81:3998- 4002 (1983)). The term "antigenic epitope," as used herein, is defined as a portion of a protein to which an antibody can immunospecifically bind its antigen as determined by any method well known in the art, for example, by the immunoassays described herein. Immunospecific binding excludes non-specific binding but does not necessarily exclude cross- reactivity with other antigens. Antigenic epitopes need not necessarily be immunogenic.

[0155] Fragments which function as epitopes may be produced by any conventional means. (See, e.g., Houghten, R. A., Proc. Natl. Acad. Sci. USA 82:5131-5135 (1985) further described in U.S. Patent No. 4,631,211.)

[0156] In the present invention, antigenic epitopes preferably contain a sequence of at least 4, at least 5, at least 6, at least 7, more preferably at least 8, at least 9, at least 10, at

least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 25, at least 30, at least 40, at least 50, and, most preferably, between about 15 to about 30 amino acids. Preferred polypeptides comprising immunogenic or antigenic epitopes are at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 amino acid residues in length. Additional non-exclusive preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as portions thereof. Antigenic epitopes are useful, for example, to raise antibodies, including monoclonal antibodies, that specifically bind the epitope. Preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these antigenic epitopes. Antigenic epitopes can be used as the target molecules in immunoassays. (See, for instance, Wilson et al., Cell 37:767-778 (1984); Sutcliffe et al., Science 219:660-666 (1983)).

[0157] Non-limiting examples of epitopes of polypeptides that can be used to generate antibodies of the invention include a polypeptide comprising, or alternatively consisting of, at least one, two, three, four, five, six or more of the portion(s) of SEQ ID NO:Y specified in column 6 of Table 1A. These polypeptide fragments have been determined to bear antigenic epitopes of the proteins of the invention by the analysis of the Jameson-Wolf antigenic index which is included in the DNAStar suite of computer programs. By "comprise" it is intended that a polypeptide contains at least one, two, three, four, five, six or more of the portion(s) of SEQ ID NO:Y shown in column 6 of Table 1A, but it may contain additional flanking residues on either the amino or carboxyl termini of the recited portion. Such additional flanking sequences are preferably sequences naturally found adjacent to the portion; i.e., contiguous sequence shown in SEQ ID NO:Y. The flanking sequence may, however, be sequences from a heterologous polypeptide, such as from another protein described herein or from a heterologous polypeptide not described herein. In particular embodiments, epitope portions of a polypeptide of the invention comprise one, two, three, or more of the portions of SEQ ID NO:Y shown in column 6 of Table 1A. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0158] Similarly, immunogenic epitopes can be used, for example, to induce antibodies according to methods well known in the art. See, for instance, Sutcliffe et al., *supra*; Wilson et al., *supra*; Chow et al., Proc. Natl. Acad. Sci. USA 82:910-914; and Bittle et al., J. Gen. Virol. 66:2347-2354 (1985). Preferred immunogenic epitopes

include the immunogenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these immunogenic epitopes. The polypeptides comprising one or more immunogenic epitopes may be presented for eliciting an antibody response together with a carrier protein, such as an albumin, to an animal system (such as rabbit or mouse), or, if the polypeptide is of sufficient length (at least about 25 amino acids), the polypeptide may be presented without a carrier. However, immunogenic epitopes comprising as few as 8 to 10 amino acids have been shown to be sufficient to raise antibodies capable of binding to, at the very least, linear epitopes in a denatured polypeptide (e.g., in Western blotting).

[0159] Epitope-bearing polypeptides of the present invention may be used to induce antibodies according to methods well known in the art including, but not limited to, *in vivo* immunization, *in vitro* immunization, and phage display methods. See, e.g., Sutcliffe et al., *supra*; Wilson et al., *supra*, and Bittle et al., J. Gen. Virol., 66:2347-2354 (1985). If *in vivo* immunization is used, animals may be immunized with free peptide; however, anti-peptide antibody titer may be boosted by coupling the peptide to a macromolecular carrier, such as keyhole limpet hemacyanin (KLH) or tetanus toxoid. For instance, peptides containing cysteine residues may be coupled to a carrier using a linker such as maleimidobenzoyl- N-hydroxysuccinimide ester (MBS), while other peptides may be coupled to carriers using a more general linking agent such as glutaraldehyde. Animals such as rabbits, rats and mice are immunized with either free or carrier- coupled peptides, for instance, by intraperitoneal and/or intradermal injection of emulsions containing about 100 μg of peptide or carrier protein and Freund's adjuvant or any other adjuvant known for stimulating an immune response. Several booster injections may be needed, for instance, at intervals of about two weeks, to provide a useful titer of anti-peptide antibody which can be detected, for example, by ELISA assay using free peptide adsorbed to a solid surface. The titer of anti-peptide antibodies in serum from an immunized animal may be increased by selection of anti-peptide antibodies, for instance, by adsorption to the peptide on a solid support and elution of the selected antibodies according to methods well known in the art.

[0160] As one of skill in the art will appreciate, and as discussed above, the polypeptides of the present invention (e.g., those comprising an immunogenic or antigenic epitope) can be fused to heterologous polypeptide sequences. For example, polypeptides of the present

invention (including fragments or variants thereof), may be fused with the constant domain of immunoglobulins (IgA, IgE, IgG, IgM), or portions thereof (CH1, CH2, CH3, or any combination thereof and portions thereof, resulting in chimeric polypeptides. By way of another non-limiting example, polypeptides and/or antibodies of the present invention (including fragments or variants thereof) may be fused with albumin (including but not limited to recombinant human serum albumin or fragments or variants thereof (see, e.g., U.S. Patent No. 5,876,969, issued March 2, 1999, EP Patent 0 413 622, and U.S. Patent No. 5,766,883, issued June 16, 1998, herein incorporated by reference in their entirety)). In a preferred embodiment, polypeptides and/or antibodies of the present invention (including fragments or variants thereof) are fused with the mature form of human serum albumin (i.e., amino acids 1 – 585 of human serum albumin as shown in Figures 1 and 2 of EP Patent 0 322 094) which is herein incorporated by reference in its entirety. In another preferred embodiment, polypeptides and/or antibodies of the present invention (including fragments or variants thereof) are fused with polypeptide fragments comprising, or alternatively consisting of, amino acid residues 1-z of human serum albumin, where z is an integer from 369 to 419, as described in U.S. Patent 5,766,883 herein incorporated by reference in its entirety. Polypeptides and/or antibodies of the present invention (including fragments or variants thereof) may be fused to either the N- or C-terminal end of the heterologous protein (e.g., immunoglobulin Fc polypeptide or human serum albumin polypeptide). Polynucleotides encoding fusion proteins of the invention are also encompassed by the invention.

[0161] Such fusion proteins as those described above may facilitate purification and may increase half-life *in vivo*. This has been shown for chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. See, e.g., EP 394,827; Traunecker et al., Nature, 331:84-86 (1988). Enhanced delivery of an antigen across the epithelial barrier to the immune system has been demonstrated for antigens (e.g., insulin) conjugated to an FcRn binding partner such as IgG or Fc fragments (see, e.g., PCT Publications WO 96/22024 and WO 99/04813). IgG Fusion proteins that have a disulfide-linked dimeric structure due to the IgG portion desulfide bonds have also been found to be more efficient in binding and neutralizing other molecules than monomeric polypeptides or fragments thereof alone. See, e.g., Fountoulakis et al., J. Biochem.,

270:3958-3964 (1995). Nucleic acids encoding the above epitopes can also be recombined with a gene of interest as an epitope tag (e.g., the hemagglutinin (HA) tag or flag tag) to aid in detection and purification of the expressed polypeptide. For example, a system described by Janknecht et al. allows for the ready purification of non-denatured fusion proteins expressed in human cell lines (Janknecht et al., 1991, Proc. Natl. Acad. Sci. USA 88:8972- 897). In this system, the gene of interest is subcloned into a vaccinia recombination plasmid such that the open reading frame of the gene is translationally fused to an amino-terminal tag consisting of six histidine residues. The tag serves as a matrix binding domain for the fusion protein. Extracts from cells infected with the recombinant vaccinia virus are loaded onto Ni2+ nitriloacetic acid-agarose column and histidine-tagged proteins can be selectively eluted with imidazole-containing buffers.

Fusion Proteins

[0162] Any polypeptide of the present invention can be used to generate fusion proteins. For example, the polypeptide of the present invention, when fused to a second protein, can be used as an antigenic tag. Antibodies raised against the polypeptide of the present invention can be used to indirectly detect the second protein by binding to the polypeptide. Moreover, because secreted proteins target cellular locations based on trafficking signals, polypeptides of the present invention which are shown to be secreted can be used as targeting molecules once fused to other proteins.

[0163] Examples of domains that can be fused to polypeptides of the present invention include not only heterologous signal sequences, but also other heterologous functional regions. The fusion does not necessarily need to be direct, but may occur through linker sequences.

[0164] In certain preferred embodiments, proteins of the invention are fusion proteins comprising an amino acid sequence that is an N and/or C- terminal deletion of a polypeptide of the invention. In preferred embodiments, the invention is directed to a fusion protein comprising an amino acid sequence that is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to a polypeptide sequence of the invention. Polynucleotides encoding these proteins are also encompassed by the invention.

[0165] Moreover, fusion proteins may also be engineered to improve characteristics of the polypeptide of the present invention. For instance, a region of additional amino acids,

particularly charged amino acids, may be added to the N-terminus of the polypeptide to improve stability and persistence during purification from the host cell or subsequent handling and storage. Also, peptide moieties may be added to the polypeptide to facilitate purification. Such regions may be removed prior to final preparation of the polypeptide. The addition of peptide moieties to facilitate handling of polypeptides are familiar and routine techniques in the art.

[0166] As one of skill in the art will appreciate that, as discussed above, polypeptides of the present invention, and epitope-bearing fragments thereof, can be combined with heterologous polypeptide sequences. For example, the polypeptides of the present invention may be fused with heterologous polypeptide sequences, for example, the polypeptides of the present invention may be fused with the constant domain of immunoglobulins (IgA, IgE, IgG, IgM) or portions thereof (CH1, CH2, CH3, and any combination thereof, including both entire domains and portions thereof), or albumin (including, but not limited to, native or recombinant human albumin or fragments or variants thereof (see, e.g., U.S. Patent No. 5,876,969, issued March 2, 1999, EP Patent 0 413 622, and U.S. Patent No. 5,766,883, issued June 16, 1998, herein incorporated by reference in their entirety)), resulting in chimeric polypeptides. For example, EP-A-O 464 533 (Canadian counterpart 2045869) discloses fusion proteins comprising various portions of constant region of immunoglobulin molecules together with another human protein or part thereof. In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties (EP-A 0232 262). Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. See, D. Bennett et al., J. Molecular Recognition 8:52-58 (1995); K. Johanson et al., J. Biol. Chem. 270:9459-9471 (1995).

[0167] Moreover, the polypeptides of the present invention can be fused to marker sequences, such as a polypeptide which facilitates purification of the fused polypeptide. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth,

CA, 91311), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Another peptide tag useful for purification, the "HA" tag, corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al., Cell 37:767 (1984).)

[0168] Additional fusion proteins of the invention may be generated through the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling"), briefly described below, and further described herein. DNA shuffling may be employed to modulate the activities of polypeptides of the invention, such methods can be used to generate polypeptides with altered activity, as well as agonists and antagonists of the polypeptides. See, generally, U.S. Patent Nos. 5,605,793; 5,811,238; 5,830,721; 5,834,252; and 5,837,458, and Patten et al., Curr. Opinion Biotechnol. 8:724-33 (1997); Harayama, Trends Biotechnol. 16(2):76-82 (1998); Hansson et al., J. Mol. Biol. 287:265-76 (1999); and Lorenzo and Blasco, Biotechniques 24(2):308-13 (1998); each of these patents and publications are hereby incorporated by reference in its entirety). In a preferred embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of a polynucleotide encoding a polypeptide of the invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc., of one or more heterologous molecules encoding a heterologous polypeptide.

[0169] Thus, any of these above fusions can be engineered using the polynucleotides or the polypeptides of the present invention.

Recombinant and Synthetic Production of Polypeptides of the Invention

[0170] The present invention also relates to vectors containing the polynucleotide of the present invention, host cells, and the production of polypeptides by synthetic and recombinant techniques. The vector may be, for example, a phage, plasmid, viral, or retroviral vector. Retroviral vectors may be replication competent or replication defective. In the latter case, viral propagation generally will occur only in complementing host cells.

[0171] The polynucleotides of the invention may be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced in a precipitate, such as a calcium phosphate precipitate, or in a complex with a charged lipid.

If the vector is a virus, it may be packaged *in vitro* using an appropriate packaging cell line and then transduced into host cells.

[0172] The polynucleotide insert should be operatively linked to an appropriate promoter, such as the phage lambda PL promoter, the *E. coli lac, trp, phoA* and *tac* promoters, the SV40 early and late promoters and promoters of retroviral LTRs, to name a few. Other suitable promoters will be known to the skilled artisan. The expression constructs will further contain sites for transcription initiation, termination, and, in the transcribed region, a ribosome binding site for translation. The coding portion of the transcripts expressed by the constructs will preferably include a translation initiating codon at the beginning and a termination codon (UAA, UGA or UAG) appropriately positioned at the end of the polypeptide to be translated.

[0173] As indicated, the expression vectors will preferably include at least one selectable marker. Such markers include dihydrofolate reductase, G418 or neomycin resistance, glutamine synthase, for eukaryotic cell culture and tetracycline, kanamycin or ampicillin resistance genes for culturing in *E. coli* and other bacteria. Representative examples of appropriate hosts include, but are not limited to, bacterial cells, such as *E. coli*, *Streptomyces* and *Salmonella typhimurium* cells; fungal cells, such as yeast cells (e.g., *Saccharomyces cerevisiae* or *Pichia pastoris* (ATCC Accession No. 201178)); insect cells such as *Drosophila* S2 and *Spodoptera* Sf9 cells; animal cells such as CHO, COS, 293, NSO and Bowes melanoma cells; and plant cells. Appropriate culture mediums and conditions for the above-described host cells are known in the art.

[0174] Among vectors preferred for use in bacteria include pQE70, pQE60 and pQE-9, available from QIAGEN, Inc.; pBluescript vectors, Phagescript vectors, pNH8A, pNH16a, pNH18A, pNH46A, available from Stratagene Cloning Systems, Inc.; and ptrc99a, pKK223-3, pKK233-3, pDR540, pRIT5 available from Pharmacia Biotech, Inc. Among preferred eukaryotic vectors are pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; and pSVK3, pBPV, pMSG and pSVL available from Pharmacia. Preferred expression vectors for use in yeast systems include, but are not limited to pYES2, pYD1, pTEF1/Zeo, pYES2/GS, pPICZ, pGAPZ, pGAPZalph, pPIC9, pPIC3.5, pHIL-D2, pHIL-S1, pPIC3.5K, pPIC9K, and PAO815 (all available from Invitrogen, Carlsbad, CA). Other suitable vectors will be readily apparent to the skilled artisan.

[0175] Vectors which use glutamine synthase (GS) or DHFR as the selectable markers can be amplified in the presence of the drugs methionine sulphoximine or methotrexate, respectively. An advantage of glutamine synthase based vectors are the availabilty of cell lines (e.g., the murine myeloma cell line, NS0) which are glutamine synthase negative. Glutamine synthase expression systems can also function in glutamine synthase expressing cells (e.g., Chinese Hamster Ovary (CHO) cells) by providing additional inhibitor to prevent the functioning of the endogenous gene. A glutamine synthase expression system and components thereof are detailed in PCT publications: WO87/04462; WO86/05807; WO89/01036; WO89/10404; and WO91/06657 which are hereby incorporated in their entireties by reference herein. Additionally, glutamine synthase expression vectors can be obtained from Lonza Biologics, Inc. (Portsmouth, NH). Expression and production of monoclonal antibodies using a GS expression system in murine myeloma cells is described in Bebbington et al., Bio/technology 10:169(1992) and in Biblia and Robinson Biotechnol. Prog. 11:1 (1995) which are herein incorporated by reference.

[0176] The present invention also relates to host cells containing the above-described vector constructs described herein, and additionally encompasses host cells containing nucleotide sequences of the invention that are operably associated with one or more heterologous control regions (e.g., promoter and/or enhancer) using techniques known of in the art. The host cell can be a higher eukaryotic cell, such as a mammalian cell (e.g., a human derived cell), or a lower eukaryotic cell, such as a yeast cell, or the host cell can be a prokaryotic cell, such as a bacterial cell. A host strain may be chosen which modulates the expression of the inserted gene sequences, or modifies and processes the gene product in the specific fashion desired. Expression from certain promoters can be elevated in the presence of certain inducers; thus expression of the genetically engineered polypeptide may be controlled. Furthermore, different host cells have characteristics and specific mechanisms for the translational and post-translational processing and modification (e.g., phosphorylation, cleavage) of proteins. Appropriate cell lines can be chosen to ensure the desired modifications and processing of the foreign protein expressed.

[0177] Introduction of the nucleic acids and nucleic acid constructs of the invention into the host cell can be effected by calcium phosphate transfection, DEAE-dextran mediated transfection, cationic lipid-mediated transfection, electroporation, transduction,

infection, or other methods. Such methods are described in many standard laboratory manuals, such as Davis et al., Basic Methods In Molecular Biology (1986). It is specifically contemplated that the polypeptides of the present invention may in fact be expressed by a host cell lacking a recombinant vector.

[0178] In addition to encompassing host cells containing the vector constructs discussed herein, the invention also encompasses primary, secondary, and immortalized host cells of vertebrate origin, particularly mammalian origin, that have been engineered to delete or replace endogenous genetic material (e.g., immune/hematopoietic antigen coding sequence), and/or to include genetic material (e.g., heterologous polynucleotide sequences) that is operably associated with immune/hematopoietic associated polynucleotides of the invention, and which activates, alters, and/or amplifies endogenous immune/hematopoietic associated polynucleotides. For example, techniques known in the art may be used to operably associate heterologous control regions (e.g., promoter and/or enhancer) and endogenous immune/hematopoietic associated polynucleotide sequences via homologous recombination (see, e.g., U.S. Patent Number 5,641,670, issued June 24, 1997; International Publication Number WO 96/29411; International Publication Number WO 94/12650; Koller et al., Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature 342:435-438 (1989), the disclosures of each of which are incorporated by reference in their entireties).

[0179] Polypeptides of the present invention can also be recovered from: products purified from natural sources, including bodily fluids, tissues and cells, whether directly isolated or cultured; products of chemical synthetic procedures; and products produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast, higher plant, insect, and mammalian cells. Depending upon the host employed in a recombinant production procedure, the polypeptides of the present invention may be glycosylated or may be non-glycosylated. In addition, polypeptides of the invention may also include an initial modified methionine residue, in some cases as a result of host-mediated processes. Thus, it is well known in the art that the N-terminal methionine encoded by the translation initiation codon generally is removed with high efficiency from any protein after translation in all eukaryotic cells. While the N-terminal methionine on most proteins also is efficiently removed in most prokaryotes, for some

proteins, this prokaryotic removal process is inefficient, depending on the nature of the amino acid to which the N-terminal methionine is covalently linked.

[0180] In one embodiment, the yeast *Pichia pastoris* is used to express polypeptides of the invention in a eukaryotic system. *Pichia pastoris* is a methylotrophic yeast which can metabolize methanol as its sole carbon source. A main step in the methanol metabolization pathway is the oxidation of methanol to formaldehyde using O_2. This reaction is catalyzed by the enzyme alcohol oxidase. In order to metabolize methanol as its sole carbon source, *Pichia pastoris* must generate high levels of alcohol oxidase due, in part, to the relatively low affinity of alcohol oxidase for O_2. Consequently, in a growth medium depending on methanol as a main carbon source, the promoter region of one of the two alcohol oxidase genes (*AOX1*) is highly active. In the presence of methanol, alcohol oxidase produced from the *AOX1* gene comprises up to approximately 30% of the total soluble protein in *Pichia pastoris*. See, Ellis, S.B., *et al., Mol. Cell. Biol.* 5:1111-21 (1985); Koutz, P.J, *et al., Yeast* 5:167-77 (1989); Tschopp, J.F., *et al., Nucl. Acids Res.* 15:3859-76 (1987). Thus, a heterologous coding sequence, such as, for example, a polynucleotide of the present invention, under the transcriptional regulation of all or part of the *AOX1* regulatory sequence is expressed at exceptionally high levels in *Pichia* yeast grown in the presence of methanol.

[0181] In one example, the plasmid vector pPIC9K is used to express DNA encoding a polypeptide of the invention, as set forth herein, in a *Pichea* yeast system essentially as described in "*Pichia* Protocols: Methods in Molecular Biology," D.R. Higgins and J. Cregg, eds. The Humana Press, Totowa, NJ, 1998. This expression vector allows expression and secretion of a polypeptide of the invention by virtue of the strong *AOX1* promoter linked to the *Pichia pastoris* alkaline phosphatase (PHO) secretory signal peptide (i.e., leader) located upstream of a multiple cloning site.

[0182] Many other yeast vectors could be used in place of pPIC9K, such as, pYES2, pYD1, pTEF1/Zeo, pYES2/GS, pPICZ, pGAPZ, pGAPZalpha, pPIC9, pPIC3.5, pHIL-D2, pHIL-S1, pPIC3.5K, and PAO815, as one skilled in the art would readily appreciate, as long as the proposed expression construct provides appropriately located signals for

transcription, translation, secretion (if desired), and the like, including an in-frame AUG as required.

[0183] In another embodiment, high-level expression of a heterologous coding sequence, such as, for example, a polynucleotide of the present invention, may be achieved by cloning the heterologous polynucleotide of the invention into an expression vector such as, for example, pGAPZ or pGAPZalpha, and growing the yeast culture in the absence of methanol.

[0184] In addition to encompassing host cells containing the vector constructs discussed herein, the invention also encompasses primary, secondary, and immortalized host cells of vertebrate origin, particularly mammalian origin, that have been engineered to delete or replace endogenous genetic material (e.g., coding sequence), and/or to include genetic material (e.g., heterologous polynucleotide sequences) that is operably associated with polynucleotides of the invention, and which activates, alters, and/or amplifies endogenous polynucleotides. For example, techniques known in the art may be used to operably associate heterologous control regions (e.g., promoter and/or enhancer) and endogenous polynucleotide sequences via homologous recombination (see, e.g., U.S. Patent No. 5,641,670, issued June 24, 1997; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al., Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature 342:435-438 (1989), the disclosures of each of which are incorporated by reference in their entireties).

[0185] In addition, polypeptides of the invention can be chemically synthesized using techniques known in the art (e.g., see Creighton, 1983, Proteins: Structures and Molecular Principles, W.H. Freeman & Co., N.Y., and Hunkapiller et al., *Nature*, 310:105-111 (1984)). For example, a polypeptide corresponding to a fragment of a polypeptide can be synthesized by use of a peptide synthesizer. Furthermore, if desired, nonclassical amino acids or chemical amino acid analogs can be introduced as a substitution or addition into the polypeptide sequence. Non-classical amino acids include, but are not limited to, to the D-isomers of the common amino acids, 2,4-diaminobutyric acid, a-amino isobutyric acid, 4-aminobutyric acid, Abu, 2-amino butyric acid, g-Abu, e-Ahx, 6-amino hexanoic acid, Aib, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosine, citrulline, homocitrulline, cysteic acid, t-butylglycine, t-

butylalanine, phenylglycine, cyclohexylalanine, b-alanine, fluoro-amino acids, designer amino acids such as b-methyl amino acids, Ca-methyl amino acids, Na-methyl amino acids, and amino acid analogs in general. Furthermore, the amino acid can be D (dextrorotary) or L (levorotary).

[0186] The invention encompasses polypeptides of the present invention which are differentially modified during or after translation, e.g., by glycosylation, acetylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to an antibody molecule or other cellular ligand, etc. Any of numerous chemical modifications may be carried out by known techniques, including but not limited, to specific chemical cleavage by cyanogen bromide, trypsin, chymotrypsin, papain, V8 protease, $NaBH_4$; acetylation, formylation, oxidation, reduction; metabolic synthesis in the presence of tunicamycin; etc.

[0187] Additional post-translational modifications encompassed by the invention include, for example, e.g., N-linked or O-linked carbohydrate chains, processing of N-terminal or C-terminal ends), attachment of chemical moieties to the amino acid backbone, chemical modifications of N-linked or O-linked carbohydrate chains, and addition or deletion of an N-terminal methionine residue as a result of procaryotic host cell expression. The polypeptides may also be modified with a detectable label, such as an enzymatic, fluorescent, isotopic or affinity label to allow for detection and isolation of the protein.

[0188] Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin; and examples of suitable radioactive material include iodine (^{121}I, ^{123}I, ^{125}I, ^{131}I), carbon (^{14}C), sulfur (^{35}S), tritium (^{3}H), indium (^{111}In, ^{112}In, ^{113m}In, ^{115m}In), technetium (^{99}Tc,^{99m}Tc), thallium (^{201}Ti), gallium (^{68}Ga, ^{67}Ga), palladium (^{103}Pd), molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F), ^{153}Sm, ^{177}Lu, ^{159}Gd, ^{149}Pm, ^{140}La, ^{175}Yb, ^{166}Ho, ^{90}Y, ^{47}Sc, ^{186}Re, ^{188}Re, ^{142}Pr, ^{105}Rh, and ^{97}Ru.

[0189] In specific embodiments, a polypeptide of the present invention or fragment or variant thereof is attached to macrocyclic chelators that associate with radiometal ions, including but not limited to, ^{177}Lu, ^{90}Y, ^{166}Ho, and ^{153}Sm, to polypeptides. In a preferred embodiment, the radiometal ion associated with the macrocyclic chelators is ^{111}In. In another preferred embodiment, the radiometal ion associated with the macrocyclic chelator is ^{90}Y. In specific embodiments, the macrocyclic chelator is 1,4,7,10-tetraazacyclododecane-N,N',N",N"'-tetraacetic acid (DOTA). In other specific embodiments, DOTA is attached to an antibody of the invention or fragment thereof via a linker molecule. Examples of linker molecules useful for conjugating DOTA to a polypeptide are commonly known in the art - see, for example, DeNardo et al., Clin Cancer Res. 4(10):2483-90 (1998); Peterson et al., Bioconjug. Chem. 10(4):553-7 (1999); and Zimmerman et al, Nucl. Med. Biol. 26(8):943-50 (1999); which are hereby incorporated by reference in their entirety.

[0190] As mentioned, the immune/hematopoietic associated proteins of the invention may be modified by either natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given immune/hematopoietic associated polypeptide. Immune/hematopoietic associated polypeptides may be branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic immune/hematopoietic associated polypeptides may result from posttranslation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphotidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES, 2nd

Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993); POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifter et al., Meth. Enzymol. 182:626-646 (1990); Rattan et al., Ann. N.Y. Acad. Sci. 663:48-62 (1992)).

[0191] Also provided by the invention are chemically modified derivatives of the polypeptides of the invention which may provide additional advantages such as increased solubility, stability and circulating time of the polypeptide, or decreased immunogenicity (see U.S. Patent No. 4,179,337). The chemical moieties for derivitization may be selected from water soluble polymers such as polyethylene glycol, ethylene glycol/propylene glycol copolymers, carboxymethylcellulose, dextran, polyvinyl alcohol and the like. The polypeptides may be modified at random positions within the molecule, or at predetermined positions within the molecule and may include one, two, three or more attached chemical moieties.

[0192] The polymer may be of any molecular weight, and may be branched or unbranched. For polyethylene glycol, the preferred molecular weight is between about 1 kDa and about 100 kDa (the term "about" indicating that in preparations of polyethylene glycol, some molecules will weigh more, some less, than the stated molecular weight) for ease in handling and manufacturing. Other sizes may be used, depending on the desired therapeutic profile (e.g., the duration of sustained release desired, the effects, if any on biological activity, the ease in handling, the degree or lack of antigenicity and other known effects of the polyethylene glycol to a therapeutic protein or analog). For example, the polyethylene glycol may have an average molecular weight of about 200, 500, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 8500, 9000, 9500, 10,000, 10,500, 11,000, 11,500, 12,000, 12,500, 13,000, 13,500, 14,000, 14,500, 15,000, 15,500, 16,000, 16,500, 17,000, 17,500, 18,000, 18,500, 19,000, 19,500, 20,000, 25,000, 30,000, 35,000, 40,000, 50,000, 55,000, 60,000, 65,000, 70,000, 75,000, 80,000, 85,000, 90,000, 95,000, or 100,000 kDa.

[0193] As noted above, the polyethylene glycol may have a branched structure. Branched polyethylene glycols are described, for example, in U.S. Patent No. 5,643,575; Morpurgo et al., Appl. Biochem. Biotechnol. 56:59-72 (1996); Vorobjev et al., Nucleosides Nucleotides 18:2745-2750 (1999); and Caliceti et al., Bioconjug. Chem. 10:638-646 (1999), the disclosures of each of which are incorporated herein by reference.

[0194] The polyethylene glycol molecules (or other chemical moieties) should be attached to the protein with consideration of effects on functional or antigenic domains of the protein. There are a number of attachment methods available to those skilled in the art, such as, for example, the method disclosed in EP 0 401 384 (coupling PEG to G-CSF), herein incorporated by reference; see also Malik et al., Exp. Hematol. 20:1028-1035 (1992), reporting pegylation of GM-CSF using tresyl chloride. For example, polyethylene glycol may be covalently bound through amino acid residues via a reactive group, such as a free amino or carboxyl group. Reactive groups are those to which an activated polyethylene glycol molecule may be bound. The amino acid residues having a free amino group may include lysine residues and the N-terminal amino acid residues; those having a free carboxyl group may include aspartic acid residues glutamic acid residues and the C-terminal amino acid residue. Sulfhydryl groups may also be used as a reactive group for attaching the polyethylene glycol molecules. Preferred for therapeutic purposes is attachment at an amino group, such as attachment at the N-terminus or lysine group.

[0195] As suggested above, polyethylene glycol may be attached to proteins via linkage to any of a number of amino acid residues. For example, polyethylene glycol can be linked to proteins via covalent bonds to lysine, histidine, aspartic acid, glutamic acid, or cysteine residues. One or more reaction chemistries may be employed to attach polyethylene glycol to specific amino acid residues (e.g., lysine, histidine, aspartic acid, glutamic acid, or cysteine) of the protein or to more than one type of amino acid residue (e.g., lysine, histidine, aspartic acid, glutamic acid, cysteine and combinations thereof) of the protein.

[0196] One may specifically desire proteins chemically modified at the N-terminus. Using polyethylene glycol as an illustration of the present composition, one may select from a variety of polyethylene glycol molecules (by molecular weight, branching, etc.), the proportion of polyethylene glycol molecules to protein (polypeptide) molecules in the reaction mix, the type of pegylation reaction to be performed, and the method of obtaining the selected N-terminally pegylated protein. The method of obtaining the N-terminally pegylated preparation (i.e., separating this moiety from other monopegylated moieties if necessary) may be by purification of the N-terminally pegylated material from a population of pegylated protein molecules. Selective proteins chemically modified at the N-terminus modification may be accomplished by reductive alkylation which exploits differential reactivity of different types of primary amino groups (lysine versus the

N-terminal) available for derivatization in a particular protein. Under the appropriate reaction conditions, substantially selective derivatization of the protein at the N-terminus with a carbonyl group containing polymer is achieved.

[0197] As indicated above, pegylation of the proteins of the invention may be accomplished by any number of means. For example, polyethylene glycol may be attached to the protein either directly or by an intervening linker. Linkerless systems for attaching polyethylene glycol to proteins are described in Delgado et al., Crit. Rev. Thera. Drug Carrier Sys. 9:249-304 (1992); Francis et al., Intern. J. of Hematol. 68:1-18 (1998); U.S. Patent No. 4,002,531; U.S. Patent No. 5,349,052; WO 95/06058; and WO 98/32466, the disclosures of each of which are incorporated herein by reference.

[0198] One system for attaching polyethylene glycol directly to amino acid residues of proteins without an intervening linker employs tresylated MPEG, which is produced by the modification of monmethoxy polyethylene glycol (MPEG) using tresylchloride ($ClSO_2CH_2CF_3$). Upon reaction of protein with tresylated MPEG, polyethylene glycol is directly attached to amine groups of the protein. Thus, the invention includes protein-polyethylene glycol conjugates produced by reacting proteins of the invention with a polyethylene glycol molecule having a 2,2,2-trifluoreothane sulphonyl group.

[0199] Polyethylene glycol can also be attached to proteins using a number of different intervening linkers. For example, U.S. Patent No. 5,612,460, the entire disclosure of which is incorporated herein by reference, discloses urethane linkers for connecting polyethylene glycol to proteins. Protein-polyethylene glycol conjugates wherein the polyethylene glycol is attached to the protein by a linker can also be produced by reaction of proteins with compounds such as MPEG-succinimidylsuccinate, MPEG activated with 1,1'-carbonyldiimidazole, MPEG-2,4,5-trichloropenylcarbonate, MPEG-p-nitrophenolcarbonate, and various MPEG-succinate derivatives. A number of additional polyethylene glycol derivatives and reaction chemistries for attaching polyethylene glycol to proteins are described in International Publication No. WO 98/32466, the entire disclosure of which is incorporated herein by reference. Pegylated protein products produced using the reaction chemistries set out herein are included within the scope of the invention.

[0200] The number of polyethylene glycol moieties attached to each protein of the invention (i.e., the degree of substitution) may also vary. For example, the pegylated

proteins of the invention may be linked, on average, to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 17, 20, or more polyethylene glycol molecules. Similarly, the average degree of substitution within ranges such as 1-3, 2-4, 3-5, 4-6, 5-7, 6-8, 7-9, 8-10, 9-11, 10-12, 11-13, 12-14, 13-15, 14-16, 15-17, 16-18, 17-19, or 18-20 polyethylene glycol moieties per protein molecule. Methods for determining the degree of substitution are discussed, for example, in Delgado et al., Crit. Rev. Thera. Drug Carrier Sys. 9:249-304 (1992).

[0201] The immune/hematopoietic associated polypeptides of the invention can be recovered and purified from chemical synthesis and recombinant cell cultures by standard methods which include, but are not limited to, ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography ("HPLC") is employed for purification. Well known techniques for refolding protein may be employed to regenerate active conformation when the polypeptide is denatured during isolation and/or purification.

[0202] Immune/hematopoietic associated polynucleotides and polypeptides may be used in accordance with the present invention for a variety of applications, particularly those that make use of the chemical and biological properties of immune/hematopoietic associated antigens. Among these are applications in the detection, prevention, diagnosis and/or treatment of diseases associated with hematopoiesis and/or the immune system, such as e.g., cancers and tumors of hematopoietic cells as well as diseases and disorders of/associated with hematopoiesis or the immune system (such as anemias, autoimmune diseases, immunodeficiencies, allergies, asthma, and inflammation) and infectious/parasitic diseases. Additional applications relate to diagnosis and to treatment of disorders of cells, tissues and organisms. These aspects of the invention are discussed further below.

[0203] In a preferred embodiment, polynucleotides expressed in a particular tissue type (see, e.g., Table 1A, column 7) are used to detect, diagnose, treat, prevent and/or prognose disorders associated with the tissue type.

[0204] The polypeptides of the invention may be in monomers or multimers (i.e., dimers, trimers, tetramers and higher multimers). Accordingly, the present invention relates to monomers and multimers of the polypeptides of the invention, their preparation,

and compositions (preferably, Therapeutics) containing them. In specific embodiments, the polypeptides of the invention are monomers, dimers, trimers or tetramers. In additional embodiments, the multimers of the invention are at least dimers, at least trimers, or at least tetramers.

[0205] Multimers encompassed by the invention may be homomers or heteromers. As used herein, the term homomer refers to a multimer containing only polypeptides corresponding to a protein of the invention (e.g., the amino acid sequence of SEQ ID NO:Y, an amino acid sequence encoded by SEQ ID NO:X or the complement of SEQ ID NO:X, the amino acid sequence encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, and/or an amino acid sequence encoded by cDNA contained in Clone ID NO:Z (including fragments, variants, splice variants, and fusion proteins, corresponding to these as described herein)). These homomers may contain polypeptides having identical or different amino acid sequences. In a specific embodiment, a homomer of the invention is a multimer containing only polypeptides having an identical amino acid sequence. In another specific embodiment, a homomer of the invention is a multimer containing polypeptides having different amino acid sequences. In specific embodiments, the multimer of the invention is a homodimer (e.g., containing two polypeptides having identical or different amino acid sequences) or a homotrimer (e.g., containing three polypeptides having identical and/or different amino acid sequences). In additional embodiments, the homomeric multimer of the invention is at least a homodimer, at least a homotrimer, or at least a homotetramer.

[0206] As used herein, the term heteromer refers to a multimer containing two or more heterologous polypeptides (i.e., polypeptides of different proteins) in addition to the polypeptides of the invention. In a specific embodiment, the multimer of the invention is a heterodimer, a heterotrimer, or a heterotetramer. In additional embodiments, the heteromeric multimer of the invention is at least a heterodimer, at least a heterotrimer, or at least a heterotetramer.

[0207] Multimers of the invention may be the result of hydrophobic, hydrophilic, ionic and/or covalent associations and/or may be indirectly linked by, for example, liposome formation. Thus, in one embodiment, multimers of the invention, such as, for example, homodimers or homotrimers, are formed when polypeptides of the invention contact one another in solution. In another embodiment, heteromultimers of the invention, such as, for

example, heterotrimers or heterotetramers, are formed when polypeptides of the invention contact antibodies to the polypeptides of the invention (including antibodies to the heterologous polypeptide sequence in a fusion protein of the invention) in solution. In other embodiments, multimers of the invention are formed by covalent associations with and/or between the polypeptides of the invention. Such covalent associations may involve one or more amino acid residues contained in the polypeptide sequence (e.g., that recited in SEQ ID NO:Y, encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, and/or encoded by the cDNA contained in Clone ID NO:Z). In one instance, the covalent associations are cross-linking between cysteine residues located within the polypeptide sequences which interact in the native (i.e., naturally occurring) polypeptide. In another instance, the covalent associations are the consequence of chemical or recombinant manipulation. Alternatively, such covalent associations may involve one or more amino acid residues contained in the heterologous polypeptide sequence in a fusion protein. In one example, covalent associations are between the heterologous sequence contained in a fusion protein of the invention (see, e.g., U.S. Patent Number 5,478,925). In a specific example, the covalent associations are between the heterologous sequence contained in a Fc fusion protein of the invention (as described herein). In another specific example, covalent associations of fusion proteins of the invention are between heterologous polypeptide sequence from another protein that is capable of forming covalently associated multimers, such as for example, osteoprotegerin (see, e.g., International Publication NO: WO 98/49305, the contents of which are herein incorporated by reference in its entirety). In another embodiment, two or more polypeptides of the invention are joined through peptide linkers. Examples include those peptide linkers described in U.S. Pat. No. 5,073,627 (hereby incorporated by reference). Proteins comprising multiple polypeptides of the invention separated by peptide linkers may be produced using conventional recombinant DNA technology.

[0208] Another method for preparing multimer polypeptides of the invention involves use of polypeptides of the invention fused to a leucine zipper or isoleucine zipper polypeptide sequence. Leucine zipper and isoleucine zipper domains are polypeptides that promote multimerization of the proteins in which they are found. Leucine zippers were originally identified in several DNA-binding proteins (Landschulz et al., Science 240:1759, (1988)), and have since been found in a variety of different proteins. Among

the known leucine zippers are naturally occurring peptides and derivatives thereof that dimerize or trimerize. Examples of leucine zipper domains suitable for producing soluble multimeric proteins of the invention are those described in PCT application WO 94/10308, hereby incorporated by reference. Recombinant fusion proteins comprising a polypeptide of the invention fused to a polypeptide sequence that dimerizes or trimerizes in solution are expressed in suitable host cells, and the resulting soluble multimeric fusion protein is recovered from the culture supernatant using techniques known in the art.

[0209] Trimeric polypeptides of the invention may offer the advantage of enhanced biological activity. Preferred leucine zipper moieties and isoleucine moieties are those that preferentially form trimers. One example is a leucine zipper derived from lung surfactant protein D (SPD), as described in Hoppe et al. (FEBS Letters 344:191, (1994)) and in U.S. patent application Ser. No. 08/446,922, hereby incorporated by reference. Other peptides derived from naturally occurring trimeric proteins may be employed in preparing trimeric polypeptides of the invention.

[0210] In another example, proteins of the invention are associated by interactions between Flag® polypeptide sequence contained in fusion proteins of the invention containing Flag® polypeptide sequence. In a further embodiment, proteins of the invention are associated by interactions between heterologous polypeptide sequence contained in Flag® fusion proteins of the invention and anti-Flag® antibody.

[0211] The multimers of the invention may be generated using chemical techniques known in the art. For example, polypeptides desired to be contained in the multimers of the invention may be chemically cross-linked using linker molecules and linker molecule length optimization techniques known in the art (see, e.g., U.S. Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Additionally, multimers of the invention may be generated using techniques known in the art to form one or more inter-molecule cross-links between the cysteine residues located within the sequence of the polypeptides desired to be contained in the multimer (see, e.g., U.S. Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Further, polypeptides of the invention may be routinely modified by the addition of cysteine or biotin to the C-terminus or N-terminus of the polypeptide and techniques known in the art may be applied to generate multimers containing one or more of these modified polypeptides (see, e.g., U.S. Patent Number 5,478,925, which is herein incorporated by reference in its entirety).

Additionally, techniques known in the art may be applied to generate liposomes containing the polypeptide components desired to be contained in the multimer of the invention (see, e.g., U.S. Patent Number 5,478,925, which is herein incorporated by reference in its entirety).

[0212] Alternatively, multimers of the invention may be generated using genetic engineering techniques known in the art. In one embodiment, polypeptides contained in multimers of the invention are produced recombinantly using fusion protein technology described herein or otherwise known in the art (see, e.g., U.S. Patent Number 5,478,925, which is herein incorporated by reference in its entirety). In a specific embodiment, polynucleotides coding for a homodimer of the invention are generated by ligating a polynucleotide sequence encoding a polypeptide of the invention to a sequence encoding a linker polypeptide and then further to a synthetic polynucleotide encoding the translated product of the polypeptide in the reverse orientation from the original C-terminus to the N-terminus (lacking the leader sequence) (see, e.g., U..S Patent Number 5,478,925, which is herein incorporated by reference in its entirety). In another embodiment, recombinant techniques described herein or otherwise known in the art are applied to generate recombinant polypeptides of the invention which contain a transmembrane domain (or hydrophobic or signal peptide) and which can be incorporated by membrane reconstitution techniques into liposomes (see, e.g., U.S. Patent Number 5,478,925, which is herein incorporated by reference in its entirety).

Antibodies

[0213] Further polypeptides of the invention relate to antibodies and T-cell antigen receptors (TCR) which immunospecifically bind a polypeptide, polypeptide fragment, or variant of the invention (e.g., a polypeptide or fragment or variant of the amino acid sequence of SEQ ID NO:Y or a polypeptide encoded by the cDNA contained in Clone ID NO:Z, and/or an epitope, of the present invention) as determined by immunoassays well known in the art for assaying specific antibody-antigen binding. Antibodies of the invention include, but are not limited to, polyclonal, monoclonal, multispecific, human, humanized or chimeric antibodies, single chain antibodies, Fab fragments, F(ab') fragments, fragments produced by a Fab expression library, anti-idiotypic (anti-Id) antibodies (including, e.g., anti-Id antibodies to antibodies of the invention),

intracellularly-made antibodies (i.e., intrabodies), and epitope-binding fragments of any of the above. The term "antibody," as used herein, refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, i.e., molecules that contain an antigen binding site that immunospecifically binds an antigen. The immunoglobulin molecules of the invention can be of any type (e.g., IgG, IgE, IgM, IgD, IgA and IgY), class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass of immunoglobulin molecule. In preferred embodiments, the immunoglobulin molecules of the invention are IgG1. In other preferred embodiments, the immunoglobulin molecules of the invention are IgG4.

[0214] Most preferably the antibodies are human antigen-binding antibody fragments of the present invention and include, but are not limited to, Fab, Fab' and F(ab')2, Fd, single-chain Fvs (scFv), single-chain antibodies, disulfide-linked Fvs (sdFv) and fragments comprising either a VL or VH domain. Antigen-binding antibody fragments, including single-chain antibodies, may comprise the variable region(s) alone or in combination with the entirety or a portion of the following: hinge region, CH1, CH2, and CH3 domains. Also included in the invention are antigen-binding fragments also comprising any combination of variable region(s) with a hinge region, CH1, CH2, and CH3 domains. The antibodies of the invention may be from any animal origin including birds and mammals. Preferably, the antibodies are human, murine (e.g., mouse and rat), donkey, ship rabbit, goat, guinea pig, camel, horse, or chicken. As used herein, "human" antibodies include antibodies having the amino acid sequence of a human immunoglobulin and include antibodies isolated from human immunoglobulin libraries or from animals transgenic for one or more human immunoglobulin and that do not express endogenous immunoglobulins, as described *infra* and, for example in, U.S. Patent No. 5,939,598 by Kucherlapati et al.

[0215] The antibodies of the present invention may be monospecific, bispecific, trispecific or of greater multispecificity. Multispecific antibodies may be specific for different epitopes of a polypeptide of the present invention or may be specific for both a polypeptide of the present invention as well as for a heterologous epitope, such as a heterologous polypeptide or solid support material. See, e.g., PCT publications WO 93/17715; WO 92/08802; WO 91/00360; WO 92/05793; Tutt, et al., J. Immunol. 147:60-

69 (1991); U.S. Patent Nos. 4,474,893; 4,714,681; 4,925,648; 5,573,920; 5,601,819; Kostelny et al., J. Immunol. 148:1547-1553 (1992).

[0216] Antibodies of the present invention may be described or specified in terms of the epitope(s) or portion(s) of a polypeptide of the present invention which they recognize or specifically bind. The epitope(s) or polypeptide portion(s) may be specified as described herein, e.g., by N-terminal and C-terminal positions, or by size in contiguous amino acid residues, or listed in the Tables and Figures. Preferred epitopes of the invention include those shown in column 6 of Table 1A, as well as polynucleotides that encode these epitopes. Antibodies which specifically bind any epitope or polypeptide of the present invention may also be excluded. Therefore, the present invention includes antibodies that specifically bind polypeptides of the present invention, and allows for the exclusion of the same.

[0217] Antibodies of the present invention may also be described or specified in terms of their cross-reactivity. Antibodies that do not bind any other analog, ortholog, or homolog of a polypeptide of the present invention are included. Antibodies that bind polypeptides with at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 65%, at least 60%, at least 55%, and at least 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In specific embodiments, antibodies of the present invention cross-react with murine, rat and/or rabbit homologs of human proteins and the corresponding epitopes thereof. Antibodies that do not bind polypeptides with less than 95%, less than 90%, less than 85%, less than 80%, less than 75%, less than 70%, less than 65%, less than 60%, less than 55%, and less than 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In a specific embodiment, the above-described cross-reactivity is with respect to any single specific antigenic or immunogenic polypeptide, or combination(s) of 2, 3, 4, 5, or more of the specific antigenic and/or immunogenic polypeptides disclosed herein. Further included in the present invention are antibodies which bind polypeptides encoded by polynucleotides which hybridize to a polynucleotide of the present invention under stringent hybridization conditions (as described herein). Antibodies of the present invention may also be described or specified in terms of their binding affinity to a polypeptide of the invention.

Preferred binding affinities include those with a dissociation constant or Kd less than 5 X 10^{-2} M, 10^{-2} M, 5 X 10^{-3} M, 10^{-3} M, 5 X 10^{-4} M, 10^{-4} M, 5 X 10^{-5} M, 10^{-5} M, 5 X 10^{-6} M, 10^{-6}M, 5 X 10^{-7} M, 10^{7} M, 5 X 10^{-8} M, 10^{-8} M, 5 X 10^{-9} M, 10^{-9} M, 5 X 10^{-10} M, 10^{-10} M, 5 X 10^{-11} M, 10^{-11} M, 5 X 10^{-12} M, 10^{-12} M, 5 X 10^{-13} M, 10^{-13} M, 5 X 10^{-14} M, 10^{-14} M, 5 X 10^{-15} M, or 10^{-15} M.

[0218] The invention also provides antibodies that competitively inhibit binding of an antibody to an epitope of the invention as determined by any method known in the art for determining competitive binding, for example, the immunoassays described herei-n. In preferred embodiments, the antibody competitively inhibits binding to the epitope by at least 95%, at least 90%, at least 85 %, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50%.

[0219] Antibodies of the present invention may act as agonists or antagonists of the polypeptides of the present invention. For example, the present invention includes antibodies which disrupt the receptor/ligand interactions with the polypeptides of the invention either partially or fully. Preferably, antibodies of the present invention bind an antigenic epitope disclosed herein, or a portion thereof. The invention features both receptor-specific antibodies and ligand-specific antibodies. The invention also features receptor-specific antibodies which do not prevent ligand binding but prevent receptor activation. Receptor activation (i.e., signaling) may be determined by techniques described herein or otherwise known in the art. For example, receptor activation can be determined by detecting the phosphorylation (e.g., tyrosine or serine/threonine) of the receptor or its substrate by immunoprecipitation followed by western blot analysis (for example, as described *supra*). In specific embodiments, antibodies are provided that inhibit ligand activity or receptor activity by at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50% of the activity in absence of the antibody.

[0220] The invention also features receptor-specific antibodies which both prevent ligand binding and receptor activation as well as antibodies that recognize the receptor-ligand complex, and, preferably, do not specifically recognize the unbound receptor or the unbound ligand. Likewise, included in the invention are neutralizing antibodies which bind the ligand and prevent binding of the ligand to the receptor, as well as antibodies which bind the ligand, thereby preventing receptor activation, but do not prevent the

ligand from binding the receptor. Further included in the invention are antibodies which activate the receptor. These antibodies may act as receptor agonists, i.e., potentiate or activate either all or a subset of the biological activities of the ligand-mediated receptor activation, for example, by inducing dimerization of the receptor. The antibodies may be specified as agonists, antagonists or inverse agonists for biological activities comprising the specific biological activities of the peptides of the invention disclosed herein. The above antibody agonists can be made using methods known in the art. See, e.g., PCT publication WO 96/40281; U.S. Patent No. 5,811,097; Deng et al., Blood 92(6):1981-1988 (1998); Chen et al., Cancer Res. 58(16):3668-3678 (1998); Harrop et al., J. Immunol. 161(4):1786-1794 (1998); Zhu et al., Cancer Res. 58(15):3209-3214 (1998); Yoon et al., J. Immunol. 160(7):3170-3179 (1998); Prat et al., J. Cell. Sci. 111(Pt2):237-247 (1998); Pitard et al., J. Immunol. Methods 205(2):177-190 (1997); Liautard et al., Cytokine 9(4):233-241 (1997); Carlson et al., J. Biol. Chem. 272(17):11295-11301 (1997); Taryman et al., Neuron 14(4):755-762 (1995); Muller et al., Structure 6(9):1153-1167 (1998); Bartunek et al., Cytokine 8(1):14-20 (1996) (which are all incorporated by reference herein in their entireties).

[0221] Antibodies of the present invention may be used, for example, to purify, detect, and target the polypeptides of the present invention, including both *in vitro* and *in vivo* diagnostic and therapeutic methods. For example, the antibodies have utility in immunoassays for qualitatively and quantitatively measuring levels of the polypeptides of the present invention in biological samples. See, e.g., Harlow et al., Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); incorporated by reference herein in its entirety.

[0222] As discussed in more detail below, the antibodies of the present invention may be used either alone or in combination with other compositions. The antibodies may further be recombinantly fused to a heterologous polypeptide at the N- or C-terminus or chemically conjugated (including covalent and non-covalent conjugations) to polypeptides or other compositions. For example, antibodies of the present invention may be recombinantly fused or conjugated to molecules useful as labels in detection assays and effector molecules such as heterologous polypeptides, drugs, radionuclides, or toxins. See, e.g., PCT publications WO 92/08495; WO 91/14438; WO 89/12624; U.S. Patent No.

5,314,995; and EP 396,387; the disclosures of which are incorporated herein by reference in their entireties.

[0223] The antibodies of the invention include derivatives that are modified, i.e., by the covalent attachment of any type of molecule to the antibody such that covalent attachment does not prevent the antibody from generating an anti-idiotypic response. For example, but not by way of limitation, the antibody derivatives include antibodies that have been modified, e.g., by glycosylation, acetylation, pegylation, phosphylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. Any of numerous chemical modifications may be carried out by known techniques, including, but not limited to specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, etc. Additionally, the derivative may contain one or more non-classical amino acids.

[0224] The antibodies of the present invention may be generated by any suitable method known in the art. Polyclonal antibodies to an antigen-of- interest can be produced by various procedures well known in the art. For example, a polypeptide of the invention can be administered to various host animals including, but not limited to, rabbits, mice, rats, etc. to induce the production of sera containing polyclonal antibodies specific for the antigen. Various adjuvants may be used to increase the immunological response, depending on the host species, and include but are not limited to, Freund's (complete and incomplete), mineral gels such as aluminum hydroxide, surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet hemocyanins, dinitrophenol, and potentially useful human adjuvants such as BCG (bacille Calmette-Guerin) and corynebacterium parvum. Such adjuvants are also well known in the art.

[0225] Monoclonal antibodies can be prepared using a wide variety of techniques known in the art including the use of hybridoma, recombinant, and phage display technologies, or a combination thereof. For example, monoclonal antibodies can be produced using hybridoma techniques including those known in the art and taught, for example, in Harlow et al., Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); Hammerling, et al., in: Monoclonal Antibodies and T-Cell Hybridomas 563-681 (Elsevier, N.Y., 1981) (said references incorporated by reference in their entireties). The term "monoclonal antibody" as used herein is not

limited to antibodies produced through hybridoma technology. The term "monoclonal antibody" refers to an antibody that is derived from a single clone, including any eukaryotic, prokaryotic, or phage clone, and not the method by which it is produced.

[0226] Methods for producing and screening for specific antibodies using hybridoma technology are routine and well known in the art and are discussed in detail in the Examples. In a non-limiting example, mice can be immunized with a polypeptide of the invention or a cell expressing such peptide. Once an immune response is detected, e.g., antibodies specific for the antigen are detected in the mouse serum, the mouse spleen is harvested and splenocytes isolated. The splenocytes are then fused by well known techniques to any suitable myeloma cells, for example cells from cell line SP20 available from the ATCC. Hybridomas are selected and cloned by limited dilution. The hybridoma clones are then assayed by methods known in the art for cells that secrete antibodies capable of binding a polypeptide of the invention. Ascites fluid, which generally contains high levels of antibodies, can be generated by immunizing mice with positive hybridoma clones.

[0227] Accordingly, the present invention provides methods of generating monoclonal antibodies as well as antibodies produced by the method comprising culturing a hybridoma cell secreting an antibody of the invention wherein, preferably, the hybridoma is generated by fusing splenocytes isolated from a mouse immunized with an antigen of the invention with myeloma cells and then screening the hybridomas resulting from the fusion for hybridoma clones that secrete an antibody able to bind a polypeptide of the invention.

[0228] Another well known method for producing both polyclonal and monoclonal human B cell lines is transformation using Epstein Barr Virus (EBV). Protocols for generating EBV-transformed B cell lines are commonly known in the art, such as, for example, the protocol outlined in Chapter 7.22 of Current Protocols in Immunology, Coligan et al., Eds., 1994, John Wiley & Sons, NY, which is hereby incorporated in its entirety by reference herein. The source of B cells for transformation is commonly human peripheral blood, but B cells for transformation may also be derived from other sources including, but not limited to, lymph nodes, tonsil, spleen, tumor tissue, and infected tissues. Tissues are generally made into single cell suspensions prior to EBV transformation. Additionally, steps may be taken to either physically remove or inactivate

T cells (e.g., by treatment with cyclosporin A) in B cell-containing samples, because T cells from individuals seropositive for anti-EBV antibodies can suppress B cell immortalization by EBV.

[0229] In general, the sample containing human B cells is innoculated with EBV, and cultured for 3-4 weeks. A typical source of EBV is the culture supernatant of the B95-8 cell line (ATCC #VR-1492). Physical signs of EBV transformation can generally be seen towards the end of the 3-4 week culture period. By phase-contrast microscopy, transformed cells may appear large, clear, hairy and tend to aggregate in tight clusters of cells. Initially, EBV lines are generally polyclonal. However, over prolonged periods of cell cultures, EBV lines may become monoclonal or polyclonal as a result of the selective outgrowth of particular B cell clones. Alternatively, polyclonal EBV transformed lines may be subcloned (e.g., by limiting dilution culture) or fused with a suitable fusion partner and plated at limiting dilution to obtain monoclonal B cell lines. Suitable fusion partners for EBV transformed cell lines include mouse myeloma cell lines (e.g., SP2/0, X63-Ag8.653), heteromyeloma cell lines (human x mouse; e.g, SPAM-8, SBC-H20, and CB-F7), and human cell lines (e.g., GM 1500, SKO-007, RPMI 8226, and KR-4). Thus, the present invention also provides a method of generating polyclonal or monoclonal human antibodies against polypeptides of the invention or fragments thereof, comprising EBV-transformation of human B cells.

[0230] Antibody fragments which recognize specific epitopes may be generated by known techniques. For example, Fab and F(ab')2 fragments of the invention may be produced by proteolytic cleavage of immunoglobulin molecules, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')2 fragments). F(ab')2 fragments contain the variable region, the light chain constant region and the CH1 domain of the heavy chain. For example, the antibodies of the present invention can also be generated using various phage display methods known in the art and as discussed in detail in the Examples (e.g., Example 10). In phage display methods, functional antibody domains are displayed on the surface of phage particles which carry the polynucleotide sequences encoding them. In a particular embodiment, such phage can be utilized to display antigen binding domains expressed from a repertoire or combinatorial antibody library (e.g., human or murine). Phage expressing an antigen binding domain that binds the antigen of interest can be selected or identified with antigen, e.g., using labeled antigen

or antigen bound or captured to a solid surface or bead. Phage used in these methods are typically filamentous phage including fd and M13 binding domains expressed from phage with Fab, Fv or disulfide stabilized Fv antibody domains recombinantly fused to either the phage gene III or gene VIII protein. Examples of phage display methods that can be used to make the antibodies of the present invention include those disclosed in Brinkman et al., J. Immunol. Methods 182:41-50 (1995); Ames et al., J. Immunol. Methods 184:177-186 (1995); Kettleborough et al., Eur. J. Immunol. 24:952-958 (1994); Persic et al., Gene 187 9-18 (1997); Burton et al., Advances in Immunology 57:191-280 (1994); PCT application No. PCT/GB91/01134; PCT publications WO 90/02809; WO 91/10737; WO 92/01047; WO 92/18619; WO 93/11236; WO 95/15982; WO 95/20401; and U.S. Patent Nos. 5,698,426; 5,223,409; 5,403,484; 5,580,717; 5,427,908; 5,750,753; 5,821,047; 5,571,698; 5,427,908; 5,516,637; 5,780,225; 5,658,727; 5,733,743 and 5,969,108; each of which is incorporated herein by reference in its entirety.

[0231] As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate whole antibodies, including human antibodies, or any other desired antigen binding fragment, and expressed in any desired host, including mammalian cells, insect cells, plant cells, yeast, and bacteria, e.g., as described in detail below. For example, techniques to recombinantly produce Fab, Fab' and F(ab')2 fragments can also be employed using methods known in the art such as those disclosed in PCT publication WO 92/22324; Mullinax et al., BioTechniques 12(6):864-869 (1992); and Sawai et al., AJRI 34:26-34 (1995); and Better et al., Science 240:1041-1043 (1988) (said references incorporated by reference in their entireties).

[0232] Examples of techniques which can be used to produce single-chain Fvs and antibodies include those described in U.S. Patents 4,946,778 and 5,258,498; Huston et al., Methods in Enzymology 203:46-88 (1991); Shu et al., PNAS 90:7995-7999 (1993); and Skerra et al., Science 240:1038-1040 (1988). For some uses, including *in vivo* use of antibodies in humans and *in vitro* detection assays, it may be preferable to use chimeric, humanized, or human antibodies. A chimeric antibody is a molecule in which different portions of the antibody are derived from different animal species, such as antibodies having a variable region derived from a murine monoclonal antibody and a human immunoglobulin constant region. Methods for producing chimeric antibodies are known

in the art. See e.g., Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Gillies et al., (1989) J. Immunol. Methods 125:191-202; U.S. Patent Nos. 5,807,715; 4,816,567; and 4,816397, which are incorporated herein by reference in their entirety. Humanized antibodies are antibody molecules from non-human species antibody that binds the desired antigen having one or more complementarity determining regions (CDRs) from the non-human species and a framework regions from a human immunoglobulin molecule. Often, framework residues in the human framework regions will be substituted with the corresponding residue from the CDR donor antibody to alter, preferably improve, antigen binding. These framework substitutions are identified by methods well known in the art, e.g., by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence comparison to identify unusual framework residues at particular positions. (See, e.g., Queen et al., U.S. Patent No. 5,585,089; Riechmann et al., Nature 332:323 (1988), which are incorporated herein by reference in their entireties.) Antibodies can be humanized using a variety of techniques known in the art including, for example, CDR-grafting (EP 239,400; PCT publication WO 91/09967; U.S. Patent Nos. 5,225,539; 5,530,101; and 5,585,089), veneering or resurfacing (EP 592,106; EP 519,596; Padlan, Molecular Immunology 28(4/5):489-498 (1991); Studnicka et al., Protein Engineering 7(6):805-814 (1994); Roguska. et al., PNAS 91:969-973 (1994)), and chain shuffling (U.S. Patent No. 5,565,332).

[0233] Completely human antibodies are particularly desirable for therapeutic treatment of human patients. Human antibodies can be made by a variety of methods known in the art including phage display methods described above using antibody libraries derived from human immunoglobulin sequences. See also, U.S. Patent Nos. 4,444,887 and 4,716,111; and PCT publications WO 98/46645, WO 98/50433, WO 98/24893, WO 98/16654, WO 96/34096, WO 96/33735, and WO 91/10741; each of which is incorporated herein by reference in its entirety.

[0234] Human antibodies can also be produced using transgenic mice which are incapable of expressing functional endogenous immunoglobulins, but which can express human immunoglobulin genes. For example, the human heavy and light chain immunoglobulin gene complexes may be introduced randomly or by homologous recombination into mouse embryonic stem cells. Alternatively, the human variable

region, constant region, and diversity region may be introduced into mouse embryonic stem cells in addition to the human heavy and light chain genes. The mouse heavy and light chain immunoglobulin genes may be rendered non-functional separately or simultaneously with the introduction of human immunoglobulin loci by homologous recombination. In particular, homozygous deletion of the JH region prevents endogenous antibody production. The modified embryonic stem cells are expanded and microinjected into blastocysts to produce chimeric mice. The chimeric mice are then bred to produce homozygous offspring which express human antibodies. The transgenic mice are immunized in the normal fashion with a selected antigen, e.g., all or a portion of a polypeptide of the invention. Monoclonal antibodies directed against the antigen can be obtained from the immunized, transgenic mice using conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA, IgM and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar, Int. Rev. Immunol. 13:65-93 (1995). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, e.g., PCT publications WO 98/24893; WO 92/01047; WO 96/34096; WO 96/33735; European Patent No. 0 598 877; U.S. Patent Nos. 5,413,923; 5,625,126; 5,633,425; 5,569,825; 5,661,016; 5,545,806; 5,814,318; 5,885,793; 5,916,771; 5,939,598; 6,075,181 and 6,114,598, which are incorporated by reference herein in their entirety. In addition, companies such as Abgenix, Inc. (Freemont, CA) and Genpharm (San Jose, CA) can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

[0235] Completely human antibodies which recognize a selected epitope can be generated using a technique referred to as "guided selection." In this approach a selected non-human monoclonal antibody, e.g., a mouse antibody, is used to guide the selection of a completely human antibody recognizing the same epitope. (Jespers et al., Bio/technology 12:899-903 (1988)).

[0236] Further, antibodies to the polypeptides of the invention can, in turn, be utilized to generate anti-idiotype antibodies that "mimic" polypeptides of the invention using

techniques well known to those skilled in the art. (See, e.g., Greenspan & Bona, FASEB J. 7(5):437-444; (1989) and Nissinoff, J. Immunol. 147(8):2429-2438 (1991)). For example, antibodies which bind to and competitively inhibit polypeptide multimerization and/or binding of a polypeptide of the invention to a ligand can be used to generate anti-idiotypes that "mimic" the polypeptide multimerization and/or binding domain and, as a consequence, bind to and neutralize polypeptide and/or its ligand. Such neutralizing anti-idiotypes or Fab fragments of such anti-idiotypes can be used in therapeutic regimens to neutralize polypeptide ligand/receptor. For example, such anti-idiotypic antibodies can be used to bind a polypeptide of the invention and/or to bind its ligand(s)/receptor(s), and thereby block its biological activity. Alternatively, antibodies which bind to and enhance polypeptide multimerization and/or binding, and/or receptor/ligand multimerization, binding and/or signaling can be used to generate anti-idiotypes that function as agonists of a polypeptide of the invention and/or its ligand/receptor. Such agonistic anti-idiotypes or Fab fragments of such anti-idiotypes can be used in therapeutic regimens as agonists of the polypeptides of the invention or its ligand(s)/receptor(s). For example, such anti-idiotypic antibodies can be used to bind a polypeptide of the invention and/or to bind its ligand(s)/receptor(s), and thereby promote or enhance its biological activity.

[0237] Intrabodies of the invention can be produced using methods known in the art, such as those disclosed and reviewed in Chen et al., Hum. Gene Ther. 5:595-601 (1994); Marasco, W.A., Gene Ther. 4:11-15 (1997); Rondon and Marasco, Annu. Rev. Microbiol. 51:257-283 (1997); Proba et al., J. Mol. Biol. 275:245-253 (1998); Cohen et al., Oncogene 17:2445-2456 (1998); Ohage and Steipe, J. Mol. Biol. 291:1119-1128 (1999); Ohage et al., J. Mol. Biol. 291:1129-1134 (1999); Wirtz and Steipe, Protein Sci. 8:2245-2250 (1999); Zhu et al., J. Immunol. Methods 231:207-222 (1999); and references cited therein.

Polynucleotides Encoding Antibodies

[0238] The invention further provides polynucleotides comprising a nucleotide sequence encoding an antibody of the invention and fragments thereof. The invention also encompasses polynucleotides that hybridize under stringent or alternatively, under lower stringency hybridization conditions, e.g., as defined *supra*, to polynucleotides that encode an antibody, preferably, that specifically binds to a polypeptide of the invention, preferably, an antibody that binds to a polypeptide having the amino acid sequence of

SEQ ID NO:Y, to a polypeptide encoded by a portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, and/or to a polypeptide encoded by the cDNA contained in Clone ID NO:Z.

[0239] The polynucleotides may be obtained, and the nucleotide sequence of the polynucleotides determined, by any method known in the art. For example, if the nucleotide sequence of the antibody is known, a polynucleotide encoding the antibody may be assembled from chemically synthesized oligonucleotides (e.g., as described in Kutmeier et al., BioTechniques 17:242 (1994)), which, briefly, involves the synthesis of overlapping oligonucleotides containing portions of the sequence encoding the antibody, annealing and ligating of those oligonucleotides, and then amplification of the ligated oligonucleotides by PCR.

[0240] Alternatively, a polynucleotide encoding an antibody may be generated from nucleic acid from a suitable source. If a clone containing a nucleic acid encoding a particular antibody is not available, but the sequence of the antibody molecule is known, a nucleic acid encoding the immunoglobulin may be chemically synthesized or obtained from a suitable source (e.g., an antibody cDNA library, or a cDNA library generated from, or nucleic acid, preferably poly A+ RNA, isolated from, any tissue or cells expressing the antibody, such as hybridoma cells selected to express an antibody of the invention) by PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of the sequence or by cloning using an oligonucleotide probe specific for the particular gene sequence to identify, e.g., a cDNA clone from a cDNA library that encodes the antibody. Amplified nucleic acids generated by PCR may then be cloned into replicable cloning vectors using any method well known in the art.

[0241] Once the nucleotide sequence and corresponding amino acid sequence of the antibody is determined, the nucleotide sequence of the antibody may be manipulated using methods well known in the art for the manipulation of nucleotide sequences, e.g., recombinant DNA techniques, site directed mutagenesis, PCR, etc. (see, for example, the techniques described in Sambrook et al., 1990, Molecular Cloning, A Laboratory Manual, 2d Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY and Ausubel et al., eds., 1998, Current Protocols in Molecular Biology, John Wiley & Sons, NY, which are both incorporated by reference herein in their entireties), to generate antibodies having a

different amino acid sequence, for example to create amino acid substitutions, deletions, and/or insertions.

[0242] In a specific embodiment, the amino acid sequence of the heavy and/or light chain variable domains may be inspected to identify the sequences of the complementarity determining regions (CDRs) by methods that are well know in the art, e.g., by comparison to known amino acid sequences of other heavy and light chain variable regions to determine the regions of sequence hypervariability. Using routine recombinant DNA techniques, one or more of the CDRs may be inserted within framework regions, e.g., into human framework regions to humanize a non-human antibody, as described *supra*. The framework regions may be naturally occurring or consensus framework regions, and preferably human framework regions (see, e.g., Chothia et al., J. Mol. Biol. 278: 457-479 (1998) for a listing of human framework regions). Preferably, the polynucleotide generated by the combination of the framework regions and CDRs encodes an antibody that specifically binds a polypeptide of the invention. Preferably, as discussed *supra*, one or more amino acid substitutions may be made within the framework regions, and, preferably, the amino acid substitutions improve binding of the antibody to its antigen. Additionally, such methods may be used to make amino acid substitutions or deletions of one or more variable region cysteine residues participating in an intrachain disulfide bond to generate antibody molecules lacking one or more intrachain disulfide bonds. Other alterations to the polynucleotide are encompassed by the present invention and within the skill of the art.

[0243] In addition, techniques developed for the production of "chimeric antibodies" (Morrison et al., Proc. Natl. Acad. Sci. 81:851-855 (1984); Neuberger et al., Nature 312:604-608 (1984); Takeda et al., Nature 314:452-454 (1985)) by splicing genes from a mouse antibody molecule of appropriate antigen specificity together with genes from a human antibody molecule of appropriate biological activity can be used. As described *supra*, a chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region, e.g., humanized antibodies.

[0244] Alternatively, techniques described for the production of single chain antibodies (U.S. Patent No. 4,946,778; Bird, Science 242:423- 42 (1988); Huston et al., Proc. Natl. Acad. Sci. USA 85:5879-5883 (1988); and Ward et al., Nature 334:544-54

(1989)) can be adapted to produce single chain antibodies. Single chain antibodies are formed by linking the heavy and light chain fragments of the Fv region via an amino acid bridge, resulting in a single chain polypeptide. Techniques for the assembly of functional Fv fragments in *E. coli* may also be used (Skerra et al., Science 242:1038- 1041 (1988)).

Methods of Producing Antibodies

[0245] The antibodies of the invention can be produced by any method known in the art for the synthesis of antibodies, in particular, by chemical synthesis or preferably, by recombinant expression techniques. Methods of producing antibodies include, but are not limited to, hybridoma technology, EBV transformation, and other methods discussed herein as well as through the use recombinant DNA technology, as discussed below.

[0246] Recombinant expression of an antibody of the invention, or fragment, derivative or analog thereof, (e.g., a heavy or light chain of an antibody of the invention or a single chain antibody of the invention), requires construction of an expression vector containing a polynucleotide that encodes the antibody. Once a polynucleotide encoding an antibody molecule or a heavy or light chain of an antibody, or portion thereof (preferably containing the heavy or light chain variable domain), of the invention has been obtained, the vector for the production of the antibody molecule may be produced by recombinant DNA technology using techniques well known in the art. Thus, methods for preparing a protein by expressing a polynucleotide containing an antibody encoding nucleotide sequence are described herein. Methods which are well known to those skilled in the art can be used to construct expression vectors containing antibody coding sequences and appropriate transcriptional and translational control signals. These methods include, for example, *in vitro* recombinant DNA techniques, synthetic techniques, and *in vivo* genetic recombination. The invention, thus, provides replicable vectors comprising a nucleotide sequence encoding an antibody molecule of the invention, or a heavy or light chain thereof, or a heavy or light chain variable domain, operably linked to a promoter. Such vectors may include the nucleotide sequence encoding the constant region of the antibody molecule (see, e.g., PCT Publication WO 86/05807; PCT Publication WO 89/01036; and U.S. Patent No. 5,122,464) and the variable domain of the antibody may be cloned into such a vector for expression of the entire heavy or light chain.

[0247] The expression vector is transferred to a host cell by conventional techniques and the transfected cells are then cultured by conventional techniques to produce an antibody of the invention. Thus, the invention includes host cells containing a polynucleotide encoding an antibody of the invention, or a heavy or light chain thereof, or a single chain antibody of the invention, operably linked to a heterologous promoter. In preferred embodiments for the expression of double-chained antibodies, vectors encoding both the heavy and light chains may be co-expressed in the host cell for expression of the entire immunoglobulin molecule, as detailed below.

[0248] A variety of host-expression vector systems may be utilized to express the antibody molecules of the invention. Such host-expression systems represent vehicles by which the coding sequences of interest may be produced and subsequently purified, but also represent cells which may, when transformed or transfected with the appropriate nucleotide coding sequences, express an antibody molecule of the invention in situ. These include but are not limited to microorganisms such as bacteria (e.g., E. coli, B. subtilis) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing antibody coding sequences; yeast (e.g., Saccharomyces, Pichia) transformed with recombinant yeast expression vectors containing antibody coding sequences; insect cell systems infected with recombinant virus expression vectors (e.g., baculovirus) containing antibody coding sequences; plant cell systems infected with recombinant virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (e.g., Ti plasmid) containing antibody coding sequences; or mammalian cell systems (e.g., COS, CHO, BHK, 293, 3T3 cells) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (e.g., metallothionein promoter) or from mammalian viruses (e.g., the adenovirus late promoter; the vaccinia virus 7.5K promoter). Preferably, bacterial cells such as Escherichia coli, and more preferably, eukaryotic cells, especially for the expression of whole recombinant antibody molecule, are used for the expression of a recombinant antibody molecule. For example, mammalian cells such as Chinese hamster ovary cells (CHO), in conjunction with a vector such as the major intermediate early gene promoter element from human cytomegalovirus is an effective expression system for antibodies (Foecking et al., Gene 45:101 (1986); Cockett et al., Bio/Technology 8:2 (1990)).

[0249] In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the antibody molecule being expressed. For example, when a large quantity of such a protein is to be produced, for the generation of pharmaceutical compositions of an antibody molecule, vectors which direct the expression of high levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited, to the E. coli expression vector pUR278 (Ruther et al., EMBO J. 2:1791 (1983)), in which the antibody coding sequence may be ligated individually into the vector in frame with the lac Z coding region so that a fusion protein is produced; pIN vectors (Inouye & Inouye, Nucleic Acids Res. 13:3101-3109 (1985); Van Heeke & Schuster, J. Biol. Chem. 24:5503-5509 (1989)); and the like. pGEX vectors may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption and binding to matrix glutathione-agarose beads followed by elution in the presence of free glutathione. The pGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

[0250] In an insect system, Autographa californica nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes. The virus grows in *Spodoptera frugiperda* cells. The antibody coding sequence may be cloned individually into non-essential regions (for example the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for example the polyhedrin promoter).

[0251] In mammalian host cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, the antibody coding sequence of interest may be ligated to an adenovirus transcription/translation control complex, e.g., the late promoter and tripartite leader sequence. This chimeric gene may then be inserted in the adenovirus genome by *in vitro* or *in vivo* recombination. Insertion in a non- essential region of the viral genome (e.g., region E1 or E3) will result in a recombinant virus that is viable and capable of expressing the antibody molecule in infected hosts. (e.g., see Logan & Shenk, Proc. Natl. Acad. Sci. USA 81:355-359 (1984)). Specific initiation signals may also be required for efficient translation of inserted antibody coding sequences. These signals include the ATG initiation codon and adjacent sequences. Furthermore, the initiation codon must be in phase with the reading frame of

the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, etc. (see Bittner et al., Methods in Enzymol. 153:51-544 (1987)).

[0252] In addition, a host cell strain may be chosen which modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications (e.g., glycosylation) and processing (e.g., cleavage) of protein products may be important for the function of the protein. Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product may be used. Such mammalian host cells include but are not limited to CHO, VERY, BHK, Hela, COS, MDCK, 293, 3T3, WI38, and in particular, breast cancer cell lines such as, for example, BT483, Hs578T, HTB2, BT20 and T47D, and normal mammary gland cell line such as, for example, CRL7030 and Hs578Bst.

[0253] For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines which stably express the antibody molecule may be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (e.g., promoter, enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may advantageously be used to engineer cell lines which express the antibody molecule. Such engineered cell lines may be particularly useful in screening and evaluation of compounds that interact directly or indirectly with the antibody molecule.

[0254] A number of selection systems may be used, including but not limited to the herpes simplex virus thymidine kinase (Wigler et al., Cell 11:223 (1977)), hypoxanthine-guanine phosphoribosyltransferase (Szybalska & Szybalski, Proc. Natl. Acad. Sci. USA 48:202 (1992)), and adenine phosphoribosyltransferase (Lowy et al., Cell 22:817 (1980)) genes can be employed in tk-, hgprt- or aprt- cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: dhfr, which confers resistance to methotrexate (Wigler et al., Natl. Acad. Sci. USA 77:357 (1980); O'Hare et al., Proc. Natl. Acad. Sci. USA 78:1527 (1981)); gpt, which confers resistance to mycophenolic acid (Mulligan & Berg, Proc. Natl. Acad. Sci. USA 78:2072 (1981)); neo, which confers resistance to the aminoglycoside G-418 Clinical Pharmacy 12:488-505; Wu and Wu, Biotherapy 3:87-95 (1991); Tolstoshev, Ann. Rev. Pharmacol. Toxicol. 32:573-596 (1993); Mulligan, Science 260:926-932 (1993); and Morgan and Anderson, Ann. Rev. Biochem. 62:191-217 (1993); TIB TECH 11(5):155-215 (1993)); and hygro, which confers resistance to hygromycin (Santerre et al., Gene 30:147 (1984)). Methods commonly known in the art of recombinant DNA technology may be routinely applied to select the desired recombinant clone, and such methods are described, for example, in Ausubel et al. (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990); and in Chapters 12 and 13, Dracopoli et al. (eds), Current Protocols in Human Genetics, John Wiley & Sons, NY (1994); Colberre-Garapin et al., J. Mol. Biol. 150:1 (1981), which are incorporated by reference herein in their entireties.

[0255] The expression levels of an antibody molecule can be increased by vector amplification (for a review, see Bebbington and Hentschel, The use of vectors based on gene amplification for the expression of cloned genes in mammalian cells in DNA cloning, Vol.3. (Academic Press, New York, 1987)). When a marker in the vector system expressing antibody is amplifiable, increase in the level of inhibitor present in culture of host cell will increase the number of copies of the marker gene. Since the amplified region is associated with the antibody gene, production of the antibody will also increase (Crouse et al., Mol. Cell. Biol. 3:257 (1983)).

[0256] Vectors which use glutamine synthase (GS) or DHFR as the selectable markers can be amplified in the presence of the drugs methionine sulphoximine or methotrexate, respectively. An advantage of glutamine synthase based vectors are the availabilty of cell

lines (e.g., the murine myeloma cell line, NS0) which are glutamine synthase negative. Glutamine synthase expression systems can also function in glutamine synthase expressing cells (e.g., Chinese Hamster Ovary (CHO) cells) by providing additional inhibitor to prevent the functioning of the endogenous gene. A glutamine synthase expression system and components thereof are detailed in PCT publications: WO87/04462; WO86/05807; WO89/01036; WO89/10404; and WO91/06657 which are incorporated in their entireties by reference herein. Additionally, glutamine synthase expression vectors that may be used according to the present invention are commercially available from suplliers, including, for example Lonza Biologics, Inc. (Portsmouth, NH). Expression and production of monoclonal antibodies using a GS expression system in murine myeloma cells is described in Bebbington et al., Bio/technology 10:169(1992) and in Biblia and Robinson Biotechnol. Prog. 11:1 (1995) which are incorporated in their entirities by reference herein.

[0257] The host cell may be co-transfected with two expression vectors of the invention, the first vector encoding a heavy chain derived polypeptide and the second vector encoding a light chain derived polypeptide. The two vectors may contain identical selectable markers which enable equal expression of heavy and light chain polypeptides. Alternatively, a single vector may be used which encodes, and is capable of expressing, both heavy and light chain polypeptides. In such situations, the light chain should be placed before the heavy chain to avoid an excess of toxic free heavy chain (Proudfoot, Nature 322:52 (1986); Kohler, Proc. Natl. Acad. Sci. USA 77:2197 (1980)). The coding sequences for the heavy and light chains may comprise cDNA or genomic DNA.

[0258] Once an antibody molecule of the invention has been produced by an animal, chemically synthesized, or recombinantly expressed, it may be purified by any method known in the art for purification of an immunoglobulin molecule, for example, by chromatography (e.g., ion exchange, affinity, particularly by affinity for the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. In addition, the antibodies of the present invention or fragments thereof can be fused to heterologous polypeptide sequences described herein or otherwise known in the art, to facilitate purification.

[0259] The present invention encompasses antibodies recombinantly fused or chemically conjugated (including both covalently and non-covalently conjugations) to a polypeptide (or portion thereof, preferably at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 amino acids of the polypeptide) of the present invention to generate fusion proteins. The fusion does not necessarily need to be direct, but may occur through linker sequences. The antibodies may be specific for antigens other than polypeptides (or portion thereof, preferably at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 amino acids of the polypeptide) of the present invention. For example, antibodies may be used to target the polypeptides of the present invention to particular cell types, either *in vitro* or *in vivo*, by fusing or conjugating the polypeptides of the present invention to antibodies specific for particular cell surface receptors. Antibodies fused or conjugated to the polypeptides of the present invention may also be used in *in vitro* immunoassays and purification methods using methods known in the art. See e.g., Harbor et al., *supra*, and PCT publication WO 93/21232; EP 439,095; Naramura et al., Immunol. Lett. 39:91-99 (1994); U.S. Patent 5,474,981; Gillies et al., PNAS 89:1428-1432 (1992); Fell et al., J. Immunol. 146:2446-2452 (1991), which are incorporated by reference in their entireties.

[0260] The present invention further includes compositions comprising the polypeptides of the present invention fused or conjugated to antibody domains other than the variable regions. For example, the polypeptides of the present invention may be fused or conjugated to an antibody Fc region, or portion thereof. The antibody portion fused to a polypeptide of the present invention may comprise the constant region, hinge region, CH1 domain, CH2 domain, and CH3 domain or any combination of whole domains or portions thereof. The polypeptides may also be fused or conjugated to the above antibody portions to form multimers. For example, Fc portions fused to the polypeptides of the present invention can form dimers through disulfide bonding between the Fc portions. Higher multimeric forms can be made by fusing the polypeptides to portions of IgA and IgM. Methods for fusing or conjugating the polypeptides of the present invention to antibody portions are known in the art. See, e.g., U.S. Patent Nos. 5,336,603; 5,622,929; 5,359,046; 5,349,053; 5,447,851; 5,112,946; EP 307,434; EP 367,166; PCT publications WO 96/04388; WO 91/06570; Ashkenazi et al., Proc. Natl. Acad. Sci. USA 88:10535-10539 (1991); Zheng et al., J. Immunol. 154:5590-5600 (1995); and Vil et al., Proc. Natl.

Acad. Sci. USA 89:11337- 11341 (1992) (said references incorporated by reference in their entireties).

[0261] As discussed, *supra*, the polypeptides corresponding to a polypeptide, polypeptide fragment, or a variant of SEQ ID NO:Y may be fused or conjugated to the above antibody portions to increase the *in vivo* half life of the polypeptides or for use in immunoassays using methods known in the art. Further, the polypeptides corresponding to SEQ ID NO:Y may be fused or conjugated to the above antibody portions to facilitate purification. One reported example describes chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. See EP 394,827; Traunecker et al., Nature 331:84-86 (1988). The polypeptides of the present invention fused or conjugated to an antibody having disulfide- linked dimeric structures (due to the IgG) may also be more efficient in binding and neutralizing other molecules, than the monomeric secreted protein or protein fragment alone. See, for example, Fountoulakis et al., J. Biochem. 270:3958-3964 (1995). In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. See, for example, EP A 232,262. Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. (See, Bennett et al., J. Molecular Recognition 8:52-58 (1995); Johanson et al., J. Biol. Chem. 270:9459-9471 (1995)).

[0262] Moreover, the antibodies or fragments thereof of the present invention can be fused to marker sequences, such as a peptide to facilitate purification. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the "HA" tag, which corresponds to an epitope derived

from the influenza hemagglutinin protein (Wilson et al., Cell 37:767 (1984)) and the "flag" tag.

[0263] The present invention further encompasses antibodies or fragments thereof conjugated to a diagnostic or therapeutic agent. The antibodies can be used diagnostically to, for example, monitor the development or progression of a tumor as part of a clinical testing procedure to, e.g., determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, radioactive materials, positron emitting metals using various positron emission tomographies, and nonradioactive paramagnetic metal ions. The detectable substance may be coupled or conjugated either directly to the antibody (or fragment thereof) or indirectly, through an intermediate (such as, for example, a linker known in the art) using techniques known in the art. See, for example, U.S. Patent No. 4,741,900 for metal ions which can be conjugated to antibodies for use as diagnostics according to the present invention.

[0264] Further, an antibody or fragment thereof may be conjugated to a therapeutic moiety such as a cytotoxin, e.g., a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example, 213Bi. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include paclitaxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclothosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis- dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine).

[0265] The conjugates of the invention can be used for modifying a given biological response, the therapeutic agent or drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor, a-interferon, ß-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent, e.g., TNF-alpha, TNF-beta, AIM I (See, International Publication No. WO 97/33899), AIM II (See, International Publication No. WO 97/34911), Fas Ligand (Takahashi *et al., Int. Immunol., 6*:1567-1574 (1994)), VEGI (See, International Publication No. WO 99/23105), a thrombotic agent or an anti- angiogenic agent, e.g., angiostatin or endostatin; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

[0266] Antibodies may also be attached to solid supports, which are particularly useful for immunoassays or purification of the target antigen. Such solid supports include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

[0267] Techniques for conjugating such therapeutic moiety to antibodies are well known. See, for example., Arnon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in Monoclonal Antibodies And Cancer Therapy, Reisfeld et al. (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug Delivery", in Controlled Drug Delivery (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in Monoclonal Antibodies '84: Biological And Clinical Applications, Pinchera et al. (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985), and Thorpe et al., "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", Immunol. Rev. 62:119-58 (1982).

[0268] Alternatively, an antibody can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Patent No. 4,676,980, which is incorporated herein by reference in its entirety.

[0269] An antibody, with or without a therapeutic moiety conjugated to it, administered alone or in combination with cytotoxic factor(s) and/or cytokine(s) can be used as a therapeutic.

Immunophenotyping

[0270] The antibodies of the invention may be utilized for immunophenotyping of cell lines and biological samples. Translation products of the genes of the present invention may be useful as cell specific markers, or more specifically as cellular markers that are differentially expressed at various stages of differentiation and/or maturation of particular cell types. Monoclonal antibodies directed against a specific epitope, or combination of epitopes, will allow for the screening of cellular populations expressing the marker. Various techniques can be utilized using monoclonal antibodies to screen for cellular populations expressing the marker(s), and include magnetic separation using antibody-coated magnetic beads, "panning" with antibody attached to a solid matrix (i.e., plate), and flow cytometry (See, e.g., U.S. Patent 5,985,660; and Morrison et al., Cell, 96:737-49 (1999)).

[0271] These techniques allow for the screening of particular populations of cells, such as might be found with hematological malignancies (i.e. minimal residual disease (MRD) in acute leukemic patients) and "non-self" cells in transplantations to prevent Graft-versus-Host Disease (GVHD). Alternatively, these techniques allow for the screening of hematopoietic stem and progenitor cells capable of undergoing proliferation and/or differentiation, as might be found in human umbilical cord blood.

Assays For Antibody Binding

[0272] The antibodies of the invention may be assayed for immunospecific binding by any method known in the art. The immunoassays which can be used include but are not limited to competitive and non-competitive assay systems using techniques such as western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion

precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, and protein A immunoassays, to name but a few. Such assays are routine and well known in the art (see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, which is incorporated by reference herein in its entirety). Exemplary immunoassays are described briefly below (but are not intended by way of limitation).

[0273] Immunoprecipitation protocols generally comprise lysing a population of cells in a lysis buffer such as RIPA buffer (1% NP-40 or Triton X- 100, 1% sodium deoxycholate, 0.1% SDS, 0.15 M NaCl, 0.01 M sodium phosphate at pH 7.2, 1% Trasylol) supplemented with protein phosphatase and/or protease inhibitors (e.g., EDTA, PMSF, aprotinin, sodium vanadate), adding the antibody of interest to the cell lysate, incubating for a period of time (e.g., 1-4 hours) at 4° C, adding protein A and/or protein G sepharose beads to the cell lysate, incubating for about an hour or more at 4° C, washing the beads in lysis buffer and resuspending the beads in SDS/sample buffer. The ability of the antibody of interest to immunoprecipitate a particular antigen can be assessed by, e.g., western blot analysis. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the binding of the antibody to an antigen and decrease the background (e.g., pre-clearing the cell lysate with sepharose beads). For further discussion regarding immunoprecipitation protocols see, e.g., Ausubel et al., eds., (1994), Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, section 10.16.1.

[0274] Western blot analysis generally comprises preparing protein samples, electrophoresis of the protein samples in a polyacrylamide gel (e.g., 8%- 20% SDS-PAGE depending on the molecular weight of the antigen), transferring the protein sample from the polyacrylamide gel to a membrane such as nitrocellulose, PVDF or nylon, blocking the membrane in blocking solution (e.g., PBS with 3% BSA or non-fat milk), washing the membrane in washing buffer (e.g., PBS-Tween 20), blocking the membrane with primary antibody (the antibody of interest) diluted in blocking buffer, washing the membrane in washing buffer, blocking the membrane with a secondary antibody (which recognizes the primary antibody, e.g., an anti-human antibody) conjugated to an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) or radioactive molecule (e.g., 32P or

125I) diluted in blocking buffer, washing the membrane in wash buffer, and detecting the presence of the antigen. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected and to reduce the background noise. For further discussion regarding western blot protocols see, e.g., Ausubel et al., eds., (1994), Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, section 10.8.1.

[0275] ELISAs comprise preparing antigen, coating the well of a 96 well microtiter plate with the antigen, adding the antibody of interest conjugated to a detectable compound such as an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) to the well and incubating for a period of time, and detecting the presence of the antigen. In ELISAs the antibody of interest does not have to be conjugated to a detectable compound; instead, a second antibody (which recognizes the antibody of interest) conjugated to a detectable compound may be added to the well. Further, instead of coating the well with the antigen, the antibody may be coated to the well. In this case, a second antibody conjugated to a detectable compound may be added following the addition of the antigen of interest to the coated well. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected as well as other variations of ELISAs known in the art. For further discussion regarding ELISAs see, e.g., Ausubel et al., eds., (1994), Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, section 11.2.1.

[0276] The binding affinity of an antibody to an antigen and the off-rate of an antibody-antigen interaction can be determined by competitive binding assays. One example of a competitive binding assay is a radioimmunoassay comprising the incubation of labeled antigen (e.g., 3H or 125I) with the antibody of interest in the presence of increasing amounts of unlabeled antigen, and the detection of the antibody bound to the labeled antigen. The affinity of the antibody of interest for a particular antigen and the binding off-rates can be determined from the data by scatchard plot analysis. Competition with a second antibody can also be determined using radioimmunoassays. In this case, the antigen is incubated with antibody of interest conjugated to a labeled compound (e.g., 3H or 125I) in the presence of increasing amounts of an unlabeled second antibody.

[0277] Antibodies of the invention may be characterized using immunocytochemisty methods on cells (e.g., mammalian cells, such as CHO cells) transfected with a vector

enabling the expression of an immune/hematopoietic antigen or with vector alone using techniques commonly known in the art. Antibodies that bind immune/hematopoietic antigen transfected cells, but not vector-only transfected cells, are immune/hematopoietic antigen specific.

Therapeutic Uses

[0278] The present invention is further directed to antibody-based therapies which involve administering antibodies of the invention to an animal, preferably a mammal, and most preferably a human, patient for treating one or more of the disclosed diseases, disorders, or conditions. Therapeutic compounds of the invention include, but are not limited to, antibodies of the invention (including fragments, analogs and derivatives thereof as described herein) and nucleic acids encoding antibodies of the invention (including fragments, analogs and derivatives thereof and anti-idiotypic antibodies as described herein). The antibodies of the invention can be used to treat, inhibit or prevent diseases, disorders or conditions associated with aberrant expression and/or activity of a polypeptide of the invention, including, but not limited to, any one or more of the diseases, disorders, or conditions described herein. The treatment and/or prevention of diseases, disorders, or conditions associated with aberrant expression and/or activity of a polypeptide of the invention includes, but is not limited to, alleviating symptoms associated with those diseases, disorders or conditions. Antibodies of the invention may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

[0279] In a specific and preferred embodiment, the present invention is directed to antibody-based therapies which involve administering antibodies of the invention to an animal, preferably a mammal, and most preferably a human, patient for treating one or more of the diseases, disorders, or conditions associated with hematopoiesis or the immune system, including, but not limited to, anemias, autoimmune diseases, immunodeficiencies, allergies, asthma, inflammation and infectious/parasitic diseases. Therapeutic compounds of the invention include, but are not limited to, antibodies of the invention (e.g., antibodies directed to the full length protein expressed on the cell surface of a mammalian cell; antibodies directed to an epitope of an immune/hematopoietic associated polypeptide of the invention (such as, a linear epitope (shown in Table 1A,

column 6) or a conformational epitope), including fragments, analogs and derivatives thereof as described herein) and nucleic acids encoding antibodies of the invention (including fragments, analogs and derivatives thereof and anti-idiotypic antibodies as described herein). The antibodies of the invention can be used to treat, inhibit or prevent diseases, disorders or conditions associated with aberrant expression and/or activity of a polypeptide of the invention, including, but not limited to, any one or more of the diseases, disorders, or conditions associated with hematopoiesis or the immune system described herein. The treatment and/or prevention of diseases, disorders, or conditions of hematopoiesis or the immune system associated with aberrant expression and/or activity of a polypeptide of the invention includes, but is not limited to, alleviating symptoms associated with those diseases, disorders or conditions. Antibodies of the invention may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

[0280] A summary of the ways in which the antibodies of the present invention may be used therapeutically includes binding polynucleotides or polypeptides of the present invention locally or systemically in the body or by direct cytotoxicity of the antibody, e.g. as mediated by complement (CDC) or by effector cells (ADCC). Some of these approaches are described in more detail below. Armed with the teachings provided herein, one of ordinary skill in the art will know how to use the antibodies of the present invention for diagnostic, monitoring or therapeutic purposes without undue experimentation.

[0281] The antibodies of this invention may be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors (such as, e.g., IL-2, IL-3 and IL-7), for example, which serve to increase the number or activity of effector cells which interact with the antibodies.

[0282] The antibodies of the invention may be administered alone or in combination with other types of treatments (e.g., radiation therapy, chemotherapy, hormonal therapy, immunotherapy and anti-tumor agents). Generally, administration of products of a species origin or species reactivity (in the case of antibodies) that is the same species as that of the patient is preferred. Thus, in a preferred embodiment, human antibodies, fragments

derivatives, analogs, or nucleic acids, are administered to a human patient for therapy or prophylaxis.

[0283] It is preferred to use high affinity and/or potent *in vivo* inhibiting and/or neutralizing antibodies against polypeptides or polynucleotides of the present invention, fragments or regions thereof, for both immunoassays directed to and therapy of disorders related to polynucleotides or polypeptides, including fragments thereof, of the present invention. Such antibodies, fragments, or regions, will preferably have an affinity for polynucleotides or polypeptides of the invention, including fragments thereof. Preferred binding affinities include those with a dissociation constant or Kd less than 5×10^{-2} M, 10^{-2} M, 5×10^{-3} M, 10^{-3} M, 5×10^{-4} M, 10^{-4} M, 5×10^{-5} M, 10^{-5} M, 5×10^{-6} M, 10^{-6} M, 5×10^{-7} M, 10^{-7} M, 5×10^{-8} M, 10^{-8} M, 5×10^{-9} M, 10^{-9} M, 5×10^{-10} M, 10^{-10} M, 5×10^{-11} M, 10^{-11} M, 5×10^{-12} M, 10^{-12} M, 5×10^{-13} M, 10^{-13} M, 5×10^{-14} M, 10^{-14} M, 5×10^{-15} M, and 10^{-15} M.

Gene Therapy

[0284] In a specific embodiment, nucleic acids comprising sequences encoding antibodies or functional derivatives thereof, are administered to treat, inhibit or prevent a disease or disorder associated with aberrant expression and/or activity of a polypeptide of the invention, by way of gene therapy. Gene therapy refers to therapy performed by the administration to a subject of an expressed or expressible nucleic acid. In this embodiment of the invention, the nucleic acids produce their encoded protein that mediates a therapeutic effect.

[0285] Any of the methods for gene therapy available in the art can be used according to the present invention. Exemplary methods are described below.

[0286] For general reviews of the methods of gene therapy, see Goldspiel et al., Clinical Pharmacy 12:488-505 (1993); Wu and Wu, Biotherapy 3:87-95 (1991); Tolstoshev, Ann. Rev. Pharmacol. Toxicol. 32:573-596 (1993); Mulligan, Science 260:926-932 (1993); and Morgan and Anderson, Ann. Rev. Biochem. 62:191-217 (1993); May, TIBTECH 11(5):155-215 (1993). Methods commonly known in the art of recombinant DNA technology which can be used are described in Ausubel et al. (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); and Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990).

[0287] In a preferred embodiment, the compound comprises nucleic acid sequences encoding an antibody, said nucleic acid sequences being part of expression vectors that express the antibody or fragments or chimeric proteins or heavy or light chains thereof in a suitable host. In particular, such nucleic acid sequences have promoters operably linked to the antibody coding region, said promoter being inducible or constitutive, and, optionally, tissue-specific. In another particular embodiment, nucleic acid molecules are used in which the antibody coding sequences and any other desired sequences are flanked by regions that promote homologous recombination at a desired site in the genome, thus providing for intrachromosomal expression of the antibody encoding nucleic acids (Koller and Smithies, Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); Zijlstra et al., Nature 342:435-438 (1989). In specific embodiments, the expressed antibody molecule is a single chain antibody; alternatively, the nucleic acid sequences include sequences encoding both the heavy and light chains, or fragments thereof, of the antibody.

[0288] Delivery of the nucleic acids into a patient may be either direct, in which case the patient is directly exposed to the nucleic acid or nucleic acid- carrying vectors, or indirect, in which case, cells are first transformed with the nucleic acids *in vitro*, then transplanted into the patient. These two approaches are known, respectively, as *in vivo* or ex vivo gene therapy.

[0289] In a specific embodiment, the nucleic acid sequences are directly administered *in vivo*, where it is expressed to produce the encoded product. This can be accomplished by any of numerous methods known in the art, e.g., by constructing them as part of an appropriate nucleic acid expression vector and administering it so that they become intracellular, e.g., by infection using defective or attenuated retrovirals or other viral vectors (see U.S. Patent No. 4,980,286), or by direct injection of naked DNA, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, encapsulation in liposomes, microparticles, or microcapsules, or by administering them in linkage to a peptide which is known to enter the nucleus, by administering it in linkage to a ligand subject to receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)) (which can be used to target cell types specifically expressing the receptors), etc. In another embodiment, nucleic acid-ligand complexes can be formed in which the ligand comprises a fusogenic viral peptide to disrupt endosomes, allowing the nucleic acid to avoid

lysosomal degradation. In yet another embodiment, the nucleic acid can be targeted *in vivo* for cell specific uptake and expression, by targeting a specific receptor (see, e.g., PCT Publications WO 92/06180; WO 92/22635; WO92/20316; WO93/14188, WO 93/20221). Alternatively, the nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination (Koller and Smithies, Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); Zijlstra et al., Nature 342:435-438 (1989)).

[0290] In a specific embodiment, viral vectors that contains nucleic acid sequences encoding an antibody of the invention are used. For example, a retroviral vector can be used (see Miller et al., Meth. Enzymol. 217:581-599 (1993)). These retroviral vectors contain the components necessary for the correct packaging of the viral genome and integration into the host cell DNA. The nucleic acid sequences encoding the antibody to be used in gene therapy are cloned into one or more vectors, which facilitates delivery of the gene into a patient. More detail about retroviral vectors can be found in Boesen et al., Biotherapy 6:291-302 (1994), which describes the use of a retroviral vector to deliver the mdr1 gene to hematopoietic stem cells in order to make the stem cells more resistant to chemotherapy. Other references illustrating the use of retroviral vectors in gene therapy are: Clowes et al., J. Clin. Invest. 93:644-651 (1994); Kiem et al., Blood 83:1467-1473 (1994); Salmons and Gunzberg, Human Gene Therapy 4:129-141 (1993); and Grossman and Wilson, Curr. Opin. in Genetics and Devel. 3:110-114 (1993).

[0291] Adenoviruses are other viral vectors that can be used in gene therapy. Adenoviruses are especially attractive vehicles for delivering genes to respiratory epithelia. Adenoviruses naturally infect respiratory epithelia where they cause a mild disease. Other targets for adenovirus-based delivery systems are liver, the central nervous system, endothelial cells, and muscle. Adenoviruses have the advantage of being capable of infecting non-dividing cells. Kozarsky and Wilson, Current Opinion in Genetics and Development 3:499-503 (1993) present a review of adenovirus-based gene therapy. Bout et al., Human Gene Therapy 5:3-10 (1994) demonstrated the use of adenovirus vectors to transfer genes to the respiratory epithelia of rhesus monkeys. Other instances of the use of adenoviruses in gene therapy can be found in Rosenfeld et al., Science 252:431-434 (1991); Rosenfeld et al., Cell 68:143- 155 (1992); Mastrangeli et al., J. Clin. Invest.

91:225-234 (1993); PCT Publication WO94/12649; and Wang, et al., Gene Therapy 2:775-783 (1995). In a preferred embodiment, adenovirus vectors are used.

[0292] Adeno-associated virus (AAV) has also been proposed for use in gene therapy (Walsh et al., Proc. Soc. Exp. Biol. Med. 204:289-300 (1993); U.S. Patent No. 5,436,146).

[0293] Another approach to gene therapy involves transferring a gene to cells in tissue culture by such methods as electroporation, lipofection, calcium phosphate mediated transfection, or viral infection. Usually, the method of transfer includes the transfer of a selectable marker to the cells. The cells are then placed under selection to isolate those cells that have taken up and are expressing the transferred gene. Those cells are then delivered to a patient.

[0294] In this embodiment, the nucleic acid is introduced into a cell prior to administration *in vivo* of the resulting recombinant cell. Such introduction can be carried out by any method known in the art, including but not limited to transfection, electroporation, microinjection, infection with a viral or bacteriophage vector containing the nucleic acid sequences, cell fusion, chromosome-mediated gene transfer, microcell-mediated gene transfer, spheroplast fusion, etc. Numerous techniques are known in the art for the introduction of foreign genes into cells (see, e.g., Loeffler and Behr, Meth. Enzymol. 217:599-618 (1993); Cohen et al., Meth. Enzymol. 217:618-644 (1993); Cline, Pharmac. Ther. 29:69-92m (1985) and may be used in accordance with the present invention, provided that the necessary developmental and physiological functions of the recipient cells are not disrupted. The technique should provide for the stable transfer of the nucleic acid to the cell, so that the nucleic acid is expressible by the cell and preferably heritable and expressible by its cell progeny.

[0295] The resulting recombinant cells can be delivered to a patient by various methods known in the art. Recombinant blood cells (e.g., hematopoietic stem or progenitor cells) are preferably administered intravenously. The amount of cells envisioned for use depends on the desired effect, patient state, etc., and can be determined by one skilled in the art.

[0296] Cells into which a nucleic acid can be introduced for purposes of gene therapy encompass any desired, available cell type, and include but are not limited to epithelial cells, endothelial cells, keratinocytes, fibroblasts, muscle cells, hepatocytes; blood cells

such as T lymphocytes, B lymphocytes, monocytes, macrophages, neutrophils, eosinophils, megakaryocytes, granulocytes; various stem or progenitor cells, in particular hematopoietic stem or progenitor cells, e.g., as obtained from bone marrow, umbilical cord blood, peripheral blood, fetal liver, etc.

[0297] In a preferred embodiment, the cell used for gene therapy is autologous to the patient.

[0298] In an embodiment in which recombinant cells are used in gene therapy, nucleic acid sequences encoding an antibody are introduced into the cells such that they are expressible by the cells or their progeny, and the recombinant cells are then administered *in vivo* for therapeutic effect. In a specific embodiment, stem or progenitor cells are used. Any stem and/or progenitor cells which can be isolated and maintained *in vitro* can potentially be used in accordance with this embodiment of the present invention (see e.g. PCT Publication WO 94/08598; Stemple and Anderson, Cell 71:973-985 (1992); Rheinwald, Meth. Cell Bio. 21A:229 (1980); and Pittelkow and Scott, Mayo Clinic Proc. 61:771 (1986)).

[0299] In a specific embodiment, the nucleic acid to be introduced for purposes of gene therapy comprises an inducible promoter operably linked to the coding region, such that expression of the nucleic acid is controllable by the presence or absence of an appropriate inducer of transcription.

Demonstration of Therapeutic or Prophylactic Activity

[0300] The compounds or pharmaceutical compositions of the invention are preferably tested *in vitro*, and then *in vivo* for the desired therapeutic or prophylactic activity, prior to use in humans. For example, *in vitro* assays to demonstrate the therapeutic or prophylactic utility of a compound or pharmaceutical composition include, the effect of a compound on a cell line or a patient tissue sample. The effect of the compound or composition on the cell line and/or tissue sample can be determined utilizing techniques known to those of skill in the art including, but not limited to, rosette formation assays and cell lysis assays. In accordance with the invention, *in vitro* assays which can be used to determine whether administration of a specific compound is indicated, include *in vitro* cell culture assays in which a patient tissue sample is grown in culture, and exposed to or

otherwise administered a compound, and the effect of such compound upon the tissue sample is observed.

Therapeutic/Prophylactic Administration and Composition

[0301] The invention provides methods of treatment, inhibition and prophylaxis by administration to a subject of an effective amount of a compound or pharmaceutical composition of the invention, preferably a polypeptide or antibody of the invention. In a preferred embodiment, the compound is substantially purified (e.g., substantially free from substances that limit its effect or produce undesired side-effects). The subject is preferably an animal, including but not limited to animals such as cows, pigs, horses, chickens, cats, dogs, etc., and is preferably a mammal, and most preferably human.

[0302] Formulations and methods of administration that can be employed when the compound comprises a nucleic acid or an immunoglobulin are described above; additional appropriate formulations and routes of administration can be selected from among those described herein below.

[0303] Various delivery systems are known and can be used to administer a compound of the invention, e.g., encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the compound, receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)), construction of a nucleic acid as part of a retroviral or other vector, etc. Methods of introduction include but are not limited to intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The compounds or compositions may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. In addition, it may be desirable to introduce the pharmaceutical compounds or compositions of the invention into the central nervous system by any suitable route, including intraventricular and intrathecal injection; intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir. Pulmonary administration can also be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

[0304] In a specific embodiment, it may be desirable to administer the pharmaceutical compounds or compositions of the invention locally to the area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion during surgery, topical application, e.g., in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. Preferably, when administering a protein, including an antibody, of the invention, care must be taken to use materials to which the protein does not absorb.

[0305] In another embodiment, the compound or composition can be delivered in a vesicle, in particular a liposome (see Langer, Science 249:1527-1533 (1990); Treat et al., in Liposomes in the Therapy of Infectious Disease and Cancer, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353- 365 (1989); Lopez-Berestein, ibid., pp. 317-327; see generally ibid.)

[0306] In yet another embodiment, the compound or composition can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, *supra*; Sefton, CRC Crit. Ref. Biomed. Eng. 14:201 (1987); Buchwald et al., Surgery 88:507 (1980); Saudek et al., N. Engl. J. Med. 321:574 (1989)). In another embodiment, polymeric materials can be used (see Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); Controlled Drug Bioavailability, Drug Product Design and Performance, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, J., Macromol. Sci. Rev. Macromol. Chem. 23:61 (1983); see also Levy et al., Science 228:190 (1985); During et al., Ann. Neurol. 25:351 (1989); Howard et al., J.Neurosurg. 71:105 (1989)). In yet another embodiment, a controlled release system can be placed in proximity of the therapeutic target, e.g., the brain, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in Medical Applications of Controlled Release, *supra*, vol. 2, pp. 115-138 (1984)).

[0307] Other controlled release systems are discussed in the review by Langer (Science 249:1527-1533 (1990)).

[0308] In a specific embodiment where the compound of the invention is a nucleic acid encoding a protein, the nucleic acid can be administered *in vivo* to promote expression of its encoded protein, by constructing it as part of an appropriate nucleic acid

expression vector and administering it so that it becomes intracellular, e.g., by use of a retroviral vector (see U.S. Patent No. 4,980,286), or by direct injection, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox- like peptide which is known to enter the nucleus (see e.g., Joliot et al., Proc. Natl. Acad. Sci. USA 88:1864-1868 (1991)), etc. Alternatively, a nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination.

[0309] The present invention also provides pharmaceutical compositions. Such compositions comprise a therapeutically effective amount of a compound, and a pharmaceutically acceptable carrier. In a specific embodiment, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin. Such compositions will contain a therapeutically effective amount of the

compound, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

[0310] In a preferred embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lignocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

[0311] The compounds of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with anions such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with cations such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

[0312] The amount of the compound of the invention which will be effective in the treatment, inhibition and prevention of a disease or disorder associated with aberrant expression and/or activity of a polypeptide of the invention can be determined by standard clinical techniques. In addition, in vitro assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

[0313] For antibodies, the dosage administered to a patient is typically 0.1 mg/kg to 100 mg/kg of the patient's body weight. Preferably, the dosage administered to a patient

is between 0.1 mg/kg and 20 mg/kg of the patient's body weight, more preferably 1 mg/kg to 10 mg/kg of the patient's body weight. Generally, human antibodies have a longer half-life within the human body than antibodies from other species due to the immune response to the foreign polypeptides. Thus, lower dosages of human antibodies and less frequent administration is often possible. Further, the dosage and frequency of administration of antibodies of the invention may be reduced by enhancing uptake and tissue penetration (e.g., into the brain) of the antibodies by modifications such as, for example, lipidation.

[0314] The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

Diagnosis and Imaging

[0315] Labeled antibodies, and derivatives and analogs thereof, which specifically bind to a polypeptide of interest can be used for diagnostic purposes to detect, diagnose, or monitor diseases, disorders, and/or conditions associated with the aberrant expression and/or activity of a polypeptide of the invention. The invention provides for the detection of aberrant expression of a polypeptide of interest, comprising (a) assaying the expression of the polypeptide of interest in cells or body fluid of an individual using one or more antibodies specific to the polypeptide interest and (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of aberrant expression.

[0316] The invention provides a diagnostic assay for diagnosing an immune/hematopoietic-related disorder, comprising (a) assaying the expression of the polypeptide of interest in cells or body fluid of an individual using one or more antibodies specific to the polypeptide interest and (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative

of a particular disorder. With respect to cancer, the presence of a relatively high amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

[0317] Antibodies of the invention can be used to assay protein levels in a biological sample using classical immunohistological methods known to those of skill in the art (e.g., see Jalkanen et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen et al., J. Cell . Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine (125I, 121I), carbon (14C), sulfur (35S), tritium (3H), indium (112In), and technetium (99Tc); luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

[0318] One facet of the invention is the detection and diagnosis of a disease or disorder associated with aberrant expression of a polypeptide of interest in an animal, preferably a mammal and most preferably a human. A preferred embodiment of the invention is the detection and diagnosis of a disease or disorder of hematopoiesis or the immune system associated with aberrant expression of an immune/hematopoietic antigen in an animal, preferably a mammal and most preferably a human. In one embodiment, diagnosis comprises: a) administering (for example, parenterally, subcutaneously, or intraperitoneally) to a subject an effective amount of a labeled molecule which specifically binds to the polypeptide of interest; b) waiting for a time interval following the administering for permitting the labeled molecule to preferentially concentrate at sites in the subject where the polypeptide is expressed (and for unbound labeled molecule to be cleared to background level); c) determining background level; and d) detecting the labeled molecule in the subject, such that detection of labeled molecule above the background level indicates that the subject has a particular disease or disorder associated with aberrant expression of the polypeptide of interest. Background level can be

determined by various methods including, comparing the amount of labeled molecule detected to a standard value previously determined for a particular system.

[0319] It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of 99mTc. The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain the specific protein. *In vivo* tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments." (Chapter 13 in Tumor Imaging: The Radiochemical Detection of Cancer, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982)).

[0320] Depending on several variables, including the type of label used and the mode of administration, the time interval following the administration for permitting the labeled molecule to preferentially concentrate at sites in the subject and for unbound labeled molecule to be cleared to background level is 6 to 48 hours or 6 to 24 hours or 6 to 12 hours. In another embodiment the time interval following administration is 5 to 20 days or 5 to 10 days.

[0321] In an embodiment, monitoring of the disease or disorder is carried out by repeating the method for diagnosing the disease or disorder, for example, one month after initial diagnosis, six months after initial diagnosis, one year after initial diagnosis, etc.

[0322] Presence of the labeled molecule can be detected in the patient using methods known in the art for *in vivo* scanning. These methods depend upon the type of label used. Skilled artisans will be able to determine the appropriate method for detecting a particular label. Methods and devices that may be used in the diagnostic methods of the invention include, but are not limited to, computed tomography (CT), whole body scan such as position emission tomography (PET), magnetic resonance imaging (MRI), and sonography.

[0323] In a specific embodiment, the molecule is labeled with a radioisotope and is detected in the patient using a radiation responsive surgical instrument (Thurston et al., U.S. Patent No. 5,441,050). In another embodiment, the molecule is labeled with a fluorescent compound and is detected in the patient using a fluorescence responsive scanning instrument. In another embodiment, the molecule is labeled with a positron

emitting metal and is detected in the patent using positron emission-tomography. In yet another embodiment, the molecule is labeled with a paramagnetic label and is detected in a patient using magnetic resonance imaging (MRI).

Kits

[0324] The present invention provides kits that can be used in the above methods. In one embodiment, a kit comprises an antibody of the invention, preferably a purified antibody, in one or more containers. In a specific embodiment, the kits of the present invention contain a substantially isolated polypeptide comprising an epitope which is specifically immunoreactive with an antibody included in the kit. Preferably, the kits of the present invention further comprise a control antibody which does not react with the polypeptide of interest. In another specific embodiment, the kits of the present invention contain a means for detecting the binding of an antibody to a polypeptide of interest (e.g., the antibody may be conjugated to a detectable substrate such as a fluorescent compound, an enzymatic substrate, a radioactive compound or a luminescent compound, or a second antibody which recognizes the first antibody may be conjugated to a detectable substrate).

[0325] In another specific embodiment of the present invention, the kit is a diagnostic kit for use in screening serum containing antibodies specific against proliferative and/or cancerous polynucleotides and polypeptides. Such a kit may include a control antibody that does not react with the polypeptide of interest. Such a kit may include a substantially isolated polypeptide antigen comprising an epitope which is specifically immunoreactive with at least one anti-polypeptide antigen antibody. Further, such a kit includes means for detecting the binding of said antibody to the antigen (e.g., the antibody may be conjugated to a fluorescent compound such as fluorescein or rhodamine which can be detected by flow cytometry). In specific embodiments, the kit may include a recombinantly produced or chemically synthesized polypeptide antigen. The polypeptide antigen of the kit may also be attached to a solid support.

[0326] In a more specific embodiment the detecting means of the above-described kit includes a solid support to which said polypeptide antigen is attached. Such a kit may also include a non-attached reporter-labeled anti-human antibody. In this embodiment, binding of the antibody to the polypeptide antigen can be detected by binding of the said reporter-labeled antibody.

[0327] In an additional embodiment, the invention includes a diagnostic kit for use in screening serum containing antigens of the polypeptide of the invention. The diagnostic kit includes a substantially isolated antibody specifically immunoreactive with polypeptide or polynucleotide antigens, and means for detecting the binding of the polynucleotide or polypeptide antigen to the antibody. In one embodiment, the antibody is attached to a solid support. In a specific embodiment, the antibody may be a monoclonal antibody. The detecting means of the kit may include a second, labeled monoclonal antibody. Alternatively, or in addition, the detecting means may include a labeled, competing antigen.

[0328] In one diagnostic configuration, test serum is reacted with a solid phase reagent having a surface-bound antigen obtained by the methods of the present invention. After binding with specific antigen antibody to the reagent and removing unbound serum components by washing, the reagent is reacted with reporter-labeled anti-human antibody to bind reporter to the reagent in proportion to the amount of bound anti-antigen antibody on the solid support. The reagent is again washed to remove unbound labeled antibody, and the amount of reporter associated with the reagent is determined. Typically, the reporter is an enzyme which is detected by incubating the solid phase in the presence of a suitable fluorometric, luminescent or colorimetric substrate (Sigma, St. Louis, MO).

[0329] The solid surface reagent in the above assay is prepared by known techniques for attaching protein material to solid support material, such as polymeric beads, dip sticks, 96-well plate or filter material. These attachment methods generally include non-specific adsorption of the protein to the support or covalent attachment of the protein, typically through a free amine group, to a chemically reactive group on the solid support, such as an activated carboxyl, hydroxyl, or aldehyde group. Alternatively, streptavidin coated plates can be used in conjunction with biotinylated antigen(s).

[0330] Thus, the invention provides an assay system or kit for carrying out this diagnostic method. The kit generally includes a support with surface-bound recombinant antigens, and a reporter-labeled anti-human antibody for detecting surface-bound anti-antigen antibody.

Uses of the Polynucleotides

[0331] Each of the polynucleotides identified herein can be used in numerous ways as reagents. The following description should be considered exemplary and utilizes known techniques.

[0332] The polynucleotides of the present invention are useful for chromosome identification. There exists an ongoing need to identify new chromosome markers, since few chromosome marking reagents, based on actual sequence data (repeat polymorphisms), are presently available. Each sequence is specifically targeted to and can hybridize with a particular location on an individual human chromosome, thus each polynucleotide of the present invention can routinely be used as a chromosome marker using techniques known in the art. Table 1A, column 8 provides the chromosome location of some of the polynucleotides of the invention.

[0333] Briefly, sequences can be mapped to chromosomes by preparing PCR primers (preferably at least 15 bp (e.g., 15-25 bp) from the sequences shown in SEQ ID NO:X. Primers can optionally be selected using computer analysis so that primers do not span more than one predicted exon in the genomic DNA. These primers are then used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids containing the human gene corresponding to SEQ ID NO:X will yield an amplified fragment.

[0334] Similarly, somatic hybrids provide a rapid method of PCR mapping the polynucleotides to particular chromosomes. Three or more clones can be assigned per day using a single thermal cycler. Moreover, sublocalization of the polynucleotides can be achieved with panels of specific chromosome fragments. Other gene mapping strategies that can be used include in situ hybridization, prescreening with labeled flow-sorted chromosomes, preselection by hybridization to construct chromosome specific-cDNA libraries, and computer mapping techniques (See, e.g., Shuler, Trends Biotechnol 16:456-459 (1998) which is hereby incorporated by reference in its entirety).

[0335] Precise chromosomal location of the polynucleotides can also be achieved using fluorescence in situ hybridization (FISH) of a metaphase chromosomal spread. This technique uses polynucleotides as short as 500 or 600 bases; however, polynucleotides 2,000-4,000 bp are preferred. For a review of this technique, see Verma et al., "Human Chromosomes: a Manual of Basic Techniques," Pergamon Press, New York (1988).

[0336] For chromosome mapping, the polynucleotides can be used individually (to mark a single chromosome or a single site on that chromosome) or in panels (for marking multiple sites and/or multiple chromosomes).

[0337] Thus, the present invention also provides a method for chromosomal localization which involves (a) preparing PCR primers from the polynucleotide sequences in Table 1A and/or Table 2 and SEQ ID NO:X and (b) screening somatic cell hybrids containing individual chromosomes.

[0338] The polynucleotides of the present invention would likewise be useful for radiation hybrid mapping, HAPPY mapping, and long range restriction mapping. For a review of these techniques and others known in the art, see, e.g. Dear, "Genome Mapping: A Practical Approach," IRL Press at Oxford University Press, London (1997); Aydin, J. Mol. Med. 77:691-694 (1999); Hacia et al., Mol. Psychiatry 3:483-492 (1998); Herrick et al., Chromosome Res. 7:409-423 (1999); Hamilton et al., Methods Cell Biol. 62:265-280 (2000); and/or Ott, J. Hered. 90:68-70 (1999), each of which is hereby incorporated by reference in its entirety.

[0339] Once a polynucleotide has been mapped to a precise chromosomal location, the physical position of the polynucleotide can be used in linkage analysis. Linkage analysis establishes coinheritance between a chromosomal location and presentation of a particular disease. (Disease mapping data are found, for example, in V. McKusick, Mendelian Inheritance in Man (available on line through Johns Hopkins University Welch Medical Library).) Column 9 of Table 1A provides an OMIM reference identification number of diseases associated with the cytologic band disclosed in column 8 of Table 1A, as determined using techniques described herein and by reference to Table 5. Assuming 1 megabase mapping resolution and one gene per 20 kb, a cDNA precisely localized to a chromosomal region associated with the disease could be one of 50-500 potential causative genes.

[0340] Thus, once coinheritance is established, differences in a polynucleotide of the invention and the corresponding gene between affected and unaffected individuals can be examined. First, visible structural alterations in the chromosomes, such as deletions or translocations, are examined in chromosome spreads or by PCR. If no structural alterations exist, the presence of point mutations are ascertained. Mutations observed in some or all affected individuals, but not in normal individuals, indicates that the mutations

may cause the disease. However, complete sequencing of the polypeptide and the corresponding gene from several normal individuals is required to distinguish the mutation from a polymorphism. If a new polymorphism is identified, this polymorphic polypeptide can be used for further linkage analysis.

[0341] Furthermore, increased or decreased expression of the gene in affected individuals as compared to unaffected individuals can be assessed using the polynucleotides of the invention. Any of these alterations (altered expression, chromosomal rearrangement, or mutation) can be used as a diagnostic or prognostic marker. Diagnostic and prognostic methods, kits and reagents encompassed by the present invention are briefly described below and more thoroughly elsewhere herein (see e.g., the sections labeled "Antibodies", "Diagnostic Assays", and "Methods for Detecting Immune/Hematopoietic-Related Disease, Including Cancer").

[0342] Thus, the invention also provides a diagnostic method useful during diagnosis of a disorder, involving measuring the expression level of polynucleotides of the present invention in cells or body fluid from an individual and comparing the measured gene expression level with a standard level of polynucleotide expression level, whereby an increase or decrease in the gene expression level compared to the standard is indicative of a disorder. Additional non-limiting examples of diagnostic methods encompassed by the present invention are more thoroughly described elsewhere herein (see, e.g., Example 12).

[0343] In still another embodiment, the invention includes a kit for analyzing samples for the presence of proliferative and/or cancerous polynucleotides derived from a test subject, as further described herein. In a general embodiment, the kit includes at least one polynucleotide probe containing a nucleotide sequence that will specifically hybridize with a polynucleotide of the invention and a suitable container. In a specific embodiment, the kit includes two polynucleotide probes defining an internal region of the polynucleotide of the invention, where each probe has one strand containing a 31'mer-end internal to the region. In a further embodiment, the probes may be useful as primers for polymerase chain reaction amplification.

[0344] Where a diagnosis of a related disorder, including, for example, diagnosis of a tumor, has already been made according to conventional methods, the present invention is useful as a prognostic indicator, whereby patients exhibiting enhanced or depressed

polynucleotide of the invention expression will experience a worse clinical outcome relative to patients expressing the gene at a level nearer the standard level.

[0345] By "measuring the expression level of polynucleotides of the invention" is intended qualitatively or quantitatively measuring or estimating the level of the polypeptide of the invention or the level of the mRNA encoding the polypeptide of the invention in a first biological sample either directly (e.g., by determining or estimating absolute protein level or mRNA level) or relatively (e.g., by comparing to the polypeptide level or mRNA level in a second biological sample). Preferably, the polypeptide level or mRNA level in the first biological sample is measured or estimated and compared to a standard polypeptide level or mRNA level, the standard being taken from a second biological sample obtained from an individual not having the related disorder or being determined by averaging levels from a population of individuals not having a related disorder. As will be appreciated in the art, once a standard polypeptide level or mRNA level is known, it can be used repeatedly as a standard for comparison.

[0346] By "biological sample" is intended any biological sample obtained from an individual, body fluid, cell line, tissue culture, or other source which contains polypeptide of the present invention or the corresponding mRNA. As indicated, biological samples include body fluids (such as semen, lymph, vaginal pool, sera, plasma, urine, synovial fluid and spinal fluid) which contain the polypeptide of the present invention, and tissue sources found to express the polypeptide of the present invention. Methods for obtaining tissue biopsies and body fluids from mammals are well known in the art. Where the biological sample is to include mRNA, a tissue biopsy is the preferred source.

[0347] The method(s) provided above may preferably be applied in a diagnostic method and/or kits in which polynucleotides and/or polypeptides of the invention are attached to a solid support. In one exemplary method, the support may be a "gene chip" or a "biological chip" as described in U.S. Patents 5,837,832, 5,874,219, and 5,856,174. Further, such a gene chip with polynucleotides of the invention attached may be used to identify polymorphisms between the isolated polynucleotide sequences of the invention, with polynucleotides isolated from a test subject. The knowledge of such polymorphisms (i.e., their location, as well as, their existence) would be beneficial in identifying disease loci for many disorders, such as for example, in neural disorders, immune system disorders, muscular disorders, reproductive disorders, gastrointestinal disorders,

pulmonary disorders, digestive disorders, cardiovascular disorders, renal disorders, proliferative disorders, and/or cancerous diseases and conditions. Such a method is described in U.S. Patents 5,858,659 and 5,856,104. The U.S. Patents referenced *supra* are hereby incorporated by reference in their entirety herein.

[0348] The present invention encompasses polynucleotides of the present invention that are chemically synthesized, or reproduced as peptide nucleic acids (PNA), or according to other methods known in the art. The use of PNAs would serve as the preferred form if the polynucleotides of the invention are incorporated onto a solid support, or gene chip. For the purposes of the present invention, a peptide nucleic acid (PNA) is a polyamide type of DNA analog and the monomeric units for adenine, guanine, thymine and cytosine are available commercially (Perceptive Biosystems). Certain components of DNA, such as phosphorus, phosphorus oxides, or deoxyribose derivatives, are not present in PNAs. As disclosed by Nielsen et al., Science 254:1497 (1991); and Egholm et al., Nature 365:666 (1993), PNAs bind specifically and tightly to complementary DNA strands and are not degraded by nucleases. In fact, PNA binds more strongly to DNA than DNA itself does. This is probably because there is no electrostatic repulsion between the two strands, and also the polyamide backbone is more flexible. Because of this, PNA/DNA duplexes bind under a wider range of stringency conditions than DNA/DNA duplexes, making it easier to perform multiplex hybridization. Smaller probes can be used than with DNA due to the strong binding. In addition, it is more likely that single base mismatches can be determined with PNA/DNA hybridization because a single mismatch in a PNA/DNA 15-mer lowers the melting point (T.sub.m) by 8°-20° C, vs. 4°-16° C for the DNA/DNA 15-mer duplex. Also, the absence of charge groups in PNA means that hybridization can be done at low ionic strengths and reduce possible interference by salt during the analysis.

[0349] The compounds of the present invention have uses which include, but are not limited to, detecting cancer in mammals. In particular the invention is useful during diagnosis of pathological cell proliferative neoplasias which include, but are not limited to: acute myelogenous leukemias including acute monocytic leukemia, acute myeloblastic leukemia, acute promyelocytic leukemia, acute myelomonocytic leukemia, acute erythroleukemia, acute megakaryocytic leukemia, and acute undifferentiated leukemia, etc.; and chronic myelogenous leukemias including chronic myelomonocytic leukemia,

chronic granulocytic leukemia, etc. Preferred mammals include monkeys, apes, cats, dogs, cows, pigs, horses, rabbits and humans. Particularly preferred are humans.

[0350] The compounds of the present invention have preferred uses which include, but are not limited to, detecting cancer of hematopoietic cells in mammals. In particular, the invention is useful during diagnosis of pathological cell proliferative neoplasias which include, but are not limited to: leukemia, acute myelogenous leukemia, chronic myelogeneous leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, acute lymphocytic anemia (ALL) Chronic lymphocyte leukemia, plasmacytomas, multiple myeloma, and Burkitt's lymphoma. Preferred mammals include monkeys, apes, cats, dogs, cows, pigs, horses, rabbits and humans. Particularly preferred are humans.

[0351] Pathological cell proliferative disorders are often associated with inappropriate activation of proto-oncogenes. (Gelmann, E. P. et al., "The Etiology of Acute Leukemia: Molecular Genetics and Viral Oncology," in Neoplastic Diseases of the Blood, Vol 1., Wiernik, P. H. et al. eds., 161-182 (1985)). Neoplasias are now believed to result from the qualitative alteration of a normal cellular gene product, or from the quantitative modification of gene expression by insertion into the chromosome of a viral sequence, by chromosomal translocation of a gene to a more actively transcribed region, or by some other mechanism. (Gelmann et al., *supra*) It is likely that mutated or altered expression of specific genes is involved in the pathogenesis of some leukemias, among other tissues and cell types. (Gelmann et al., *supra*) Indeed, the human counterparts of the oncogenes involved in some animal neoplasias have been amplified or translocated in some cases of human leukemia and carcinoma. (Gelmann et al., *supra*)

[0352] For example, c-myc expression is highly amplified in the non-lymphocytic leukemia cell line HL-60. When HL-60 cells are chemically induced to stop proliferation, the level of c-myc is found to be downregulated. (International Publication Number WO 91/15580). However, it has been shown that exposure of HL-60 cells to a DNA construct that is complementary to the 5' end of c-myc or c-myb blocks translation of the corresponding mRNAs which downregulates expression of the c-myc or c-myb proteins and causes arrest of cell proliferation and differentiation of the treated cells. (International Publication Number WO 91/15580; Wickstrom et al., Proc. Natl. Acad. Sci. 85:1028 (1988); Anfossi et al., Proc. Natl. Acad. Sci. 86:3379 (1989)). However, the skilled artisan would appreciate the present invention's usefulness is not be limited to treatment,

prevention, diagnosis and/or prognosis, of proliferative disorders of cells and tissues of hematopoietic origin, in light of the numerous cells and cell types of varying origins which are known to exhibit proliferative phenotypes. In preferred embodiments, the compounds and/or methods of the invention are used to treat, prevent, diagnose, and/or prognose, proliferative disorders of hematopoietic cells and tissues as well as cells and tissues of the immune system.

[0353] In addition to the foregoing, a polynucleotide of the present invention can be used to control gene expression through triple helix formation or through antisense DNA or RNA. Antisense techniques are discussed, for example, in Okano, J. Neurochem. 56: 560 (1991); "Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Triple helix formation is discussed in, for instance Lee et al., Nucleic Acids Research 6: 3073 (1979); Cooney et al., Science 241: 456 (1988); and Dervan et al., Science 251: 1360 (1991). Both methods rely on binding of the polynucleotide to a complementary DNA or RNA. For these techniques, preferred polynucleotides are usually oligonucleotides 20 to 40 bases in length and complementary to either the region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res. 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1360 (1991)) or to the mRNA itself (antisense - Okano, J. Neurochem. 56:560 (1991); Oligodeoxy-nucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988).) Triple helix formation optimally results in a shut-off of RNA transcription from DNA, while antisense RNA hybridization blocks translation of an mRNA molecule into polypeptide. The oligonucleotide described above can also be delivered to cells such that the antisense RNA or DNA may be expressed *in vivo* to inhibit production of polypeptide of the present invention antigens. Both techniques are effective in model systems, and the information disclosed herein can be used to design antisense or triple helix polynucleotides in an effort to treat disease, and in particular, for the treatment of proliferative diseases and/or conditions. Non-limiting antisense and triple helix methods encompassed by the present invention are more thoroughly described elsewhere herein (see, e.g., the section labeled "Antisense and Ribozyme (Antagonists)").

[0354] Polynucleotides of the present invention are also useful in gene therapy. One goal of gene therapy is to insert a normal gene into an organism having a defective gene, in an effort to correct the genetic defect. The polynucleotides disclosed in the present

invention offer a means of targeting such genetic defects in a highly accurate manner. Another goal is to insert a new gene that was not present in the host genome, thereby producing a new trait in the host cell. Additional non-limiting examples of gene therapy methods encompassed by the present invention are more thoroughly described elsewhere herein (see, e.g., the sections labeled "Gene Therapy Methods" and Examples 16, 17 and 18).

[0355] The polynucleotides are also useful for identifying individuals from minute biological samples. The United States military, for example, is considering the use of restriction fragment length polymorphism (RFLP) for identification of its personnel. In this technique, an individual's genomic DNA is digested with one or more restriction enzymes, and probed on a Southern blot to yield unique bands for identifying personnel. This method does not suffer from the current limitations of "Dog Tags" which can be lost, switched, or stolen, making positive identification difficult. The polynucleotides of the present invention can be used as additional DNA markers for RFLP.

[0356] The polynucleotides of the present invention can also be used as an alternative to RFLP, by determining the actual base-by-base DNA sequence of selected portions of an individual's genome. These sequences can be used to prepare PCR primers for amplifying and isolating such selected DNA, which can then be sequenced. Using this technique, individuals can be identified because each individual will have a unique set of DNA sequences. Once an unique ID database is established for an individual, positive identification of that individual, living or dead, can be made from extremely small tissue samples.

[0357] Forensic biology also benefits from using DNA-based identification techniques as disclosed herein. DNA sequences taken from very small biological samples such as tissues, e.g., hair or skin, or body fluids, e.g., blood, saliva, semen, synovial fluid, amniotic fluid, breast milk, lymph, pulmonary sputum or surfactant, urine, fecal matter, etc., can be amplified using PCR. In one prior art technique, gene sequences amplified from polymorphic loci, such as DQa class II HLA gene, are used in forensic biology to identify individuals. (Erlich, H., PCR Technology, Freeman and Co. (1992).) Once these specific polymorphic loci are amplified, they are digested with one or more restriction enzymes, yielding an identifying set of bands on a Southern blot probed with DNA

corresponding to the DQa class II HLA gene. Similarly, polynucleotides of the present invention can be used as polymorphic markers for forensic purposes.

[0358] There is also a need for reagents capable of identifying the source of a particular tissue. Such need arises, for example, in forensics when presented with tissue of unknown origin. Appropriate reagents can comprise, for example, DNA probes or primers prepared from the sequences of the present invention, specific to tissues, including but not limited to, those sequences referred to in Table 1A. Panels of such reagents can identify tissue by species and/or by organ type. In a similar fashion, these reagents can be used to screen tissue cultures for contamination. Additional non-limiting examples of such uses are further described herein.

[0359] Because immune/hematopoietic antigens are found expressed in hematopoietic tissues (e.g., bone marrow, fetal liver, and fetal spleen) or cells and tissues of the immune system (e.g., lymph nodes, spleen, B cells, T cells, monocytes, macrophages, dendritic cells, neutrophils, mast cells, basophils, and eosinophils), the polynucleotides of the present invention are also useful as hybridization probes for differential identification of the tissue(s) or cell type(s) present in a biological sample. Similarly, polypeptides and antibodies directed to polypeptides of the present invention are useful to provide immunological probes for differential identification of the tissue(s) (e.g., immunohistochemistry assays) or cell type(s) (e.g., immunocytochemistry assays). In a specific embodiment, the polynucleotides of the present invention are also useful as hybridization probes for differential identification of immune/hematopoietic tissue(s) or cell type(s) present in a biological sample. Similarly, polypeptides and antibodies directed to polypeptides of the present invention are useful to provide immunological probes for differential identification of immune/hematopoietic tissue(s) (e.g., immunohistochemistry assays) or cell type(s) (e.g., immunocytochemistry assays). In addition, for a number of disorders of the above tissues or cells, significantly higher or lower levels of gene expression of the polynucleotides/polypeptides of the present invention may be detected in certain tissues (e.g., tissues expressing polypeptides and/or polynucleotides of the present invention, for example, normal immune/hematopoietic or diseased immune/hematopoietic tissues, and/or those tissues/cells corresponding to the library source relating to a polynucleotide sequence of the invention as disclosed in column 7 of Table 1A, and/or cancerous and/or wounded tissues) or bodily fluids (e.g., semen, lymph, vaginal pool,

serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to a "standard" gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

[0360] Thus, the invention provides a diagnostic method of a disorder, which involves: (a) assaying gene expression level in cells or body fluid of an individual; (b) comparing the gene expression level with a standard gene expression level, whereby an increase or decrease in the assayed gene expression level compared to the standard expression level is indicative of a disorder.

[0361] In the very least, the polynucleotides of the present invention can be used as molecular weight markers on Southern gels, as diagnostic probes for the presence of a specific mRNA in a particular cell type, as a probe to "subtract-out" known sequences in the process of discovering novel polynucleotides, for selecting and making oligomers for attachment to a "gene chip" or other support, to raise anti-DNA antibodies using DNA immunization techniques, and as an antigen to elicit an immune response.

Uses of the Polypeptides

[0362] Each of the polypeptides identified herein can be used in numerous ways. The following description should be considered exemplary and utilizes known techniques.

[0363] Polypeptides and antibodies directed to polypeptides of the present invention are useful to provide immunological probes for differential identification of the tissue(s) (e.g., immunohistochemistry assays such as, for example, ABC immunoperoxidase (Hsu et al., J. Histochem. Cytochem. 29:577-580 (1981)) or cell type(s) (e.g., immunocytochemistry assays).

[0364] Antibodies can be used to assay levels of polypeptides encoded by polynucleotides of the invention in a biological sample using classical immunohistological methods known to those of skill in the art (see, e.g., Jalkanen, et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, et al., J. Cell. Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine (^{131}I, ^{125}I, ^{123}I, ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^{3}H), indium (^{115m}In, ^{113m}In, ^{112}In, ^{111}In), and technetium

(^{99}Tc, ^{99m}Tc), thallium (^{201}Ti), gallium (^{68}Ga, ^{67}Ga), palladium (^{103}Pd), molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F), ^{153}Sm, ^{177}Lu, ^{159}Gd, ^{149}Pm, ^{140}La, ^{175}Yb, ^{166}Ho, ^{90}Y, ^{47}Sc, ^{186}Re, ^{188}Re, ^{142}Pr, ^{105}Rh, ^{97}Ru; luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

[0365] In addition to assaying levels of polypeptide of the present invention in a biological sample, proteins can also be detected *in vivo* by imaging. Antibody labels or markers for *in vivo* imaging of protein include those detectable by X-radiography, NMR or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be incorporated into the antibody by labeling of nutrients for the relevant hybridoma.

[0366] An immune/hematopoietic antigen-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example, ^{131}I, ^{112}In, ^{99m}Tc, (^{131}I, ^{125}I, ^{123}I, ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^{3}H), indium (^{115m}In, ^{113m}In, ^{112}In, ^{111}In), and technetium (^{99}Tc, ^{99m}Tc), thallium (^{201}Ti), gallium (^{68}Ga, ^{67}Ga), palladium (^{103}Pd), molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F, ^{153}Sm, ^{177}Lu, ^{159}Gd, ^{149}Pm, ^{140}La, ^{175}Yb, ^{166}Ho, ^{90}Y, ^{47}Sc, ^{186}Re, ^{188}Re, ^{142}Pr, ^{105}Rh, ^{97}Ru), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (for example, parenterally, subcutaneously or intraperitoneally) into the mammal to be examined for an immune system or hematopoietic disorder. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of ^{99m}Tc. The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which express the polypeptide encoded by a polynucleotide of the invention. *In vivo* tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments" (Chapter 13 in *Tumor Imaging: The Radiochemical Detection of Cancer*, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982)).

[0367] In one embodiment, the invention provides a method for the specific delivery of compositions of the invention to cells by administering polypeptides of the invention (e.g., polypeptides encoded by polynucleotides of the invention and/or antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a therapeutic protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

[0368] In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention in association with toxins or cytotoxic prodrugs.

[0369] In a preferred embodiment, the invention provides a method for the specific destruction of immune/hematopoietic cells (e.g., aberrant immune/hematopoietic cells, immune/hematopoietic neoplasm) by administering polypeptides of the invention (e.g., polypeptides encoded by polynucleotides of the invention and/or antibodies) in association with toxins or cytotoxic prodrugs. In another preferred embodiment the invention provides a method for the specific destruction of tissues/cells corresponding to the library source relating to a polynucleotide sequence of the invention as disclosed in column 7 of Table 1A by administering polypeptides of the invention in association with toxins or cytotoxic prodrugs.

[0370] By "toxin" is meant one or more compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNAse, alpha toxin, ricin, abrin, *Pseudomonas* exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin. "Toxin" also includes a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example, ^{213}Bi, or other

radioisotopes such as, for example, ^{103}Pd, ^{133}Xe, ^{131}I, ^{111}In, ^{68}Ge, ^{57}Co, ^{65}Zn, ^{85}Sr, ^{32}P, ^{35}S, ^{90}Y, ^{153}Sm, ^{153}Gd, ^{169}Yb, ^{51}Cr, ^{54}Mn, ^{75}Se, ^{113}Sn, ^{90}Yttrium, ^{117}Tin, ^{186}Rhenium, ^{166}Holmium, and ^{188}Rhenium; luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

[0371] In a specific embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention or antibodies of the invention in association with the radioisotope ^{90}Y. In another specific embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention or antibodies of the invention in association with the radioisotope ^{111}In. In a further specific embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention or antibodies of the invention in association with the radioisotope ^{131}I.

[0372] Techniques known in the art may be applied to label polypeptides of the invention (including antibodies). Such techniques include, but are not limited to, the use of bifunctional conjugating agents (see e.g., U.S. Patent Nos. 5,756,065; 5,714,631; 5,696,239; 5,652,361; 5,505,931; 5,489,425; 5,435,990; 5,428,139; 5,342,604; 5,274,119; 4,994,560; and 5,808,003; the contents of each of which are hereby incorporated by reference in its entirety).

[0373] Thus, the invention provides a diagnostic method of a disorder, which involves (a) assaying the expression level of a polypeptide of the present invention in cells or body fluid of an individual; and (b) comparing the assayed polypeptide expression level with a standard polypeptide expression level, whereby an increase or decrease in the assayed polypeptide expression level compared to the standard expression level is indicative of a disorder. With respect to cancer, the presence of a relatively high amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

[0374] Moreover, polypeptides of the present invention can be used to treat or prevent diseases or conditions of/assocatied with hematopoiesis and/or the immune system such

as, for example, such as anemias, autoimmune diseases, immunodeficiencies, allergies, asthma, and inflammation) and infectious/parasitic diseases. In preferred embodiments, polynucleotides expressed in a particular tissue type (see, e.g., Table 1A, column 7) are used to diagnose, detect, prevent, treat and/or prognose disorders associated with the tissue type. For example, patients can be administered a polypeptide of the present invention in an effort to replace absent or decreased levels of the polypeptide (e.g., insulin), to supplement absent or decreased levels of a different polypeptide (e.g., hemoglobin S for hemoglobin B, SOD, catalase, DNA repair proteins), to inhibit the activity of a polypeptide (e.g., an oncogene or tumor supressor), to activate the activity of a polypeptide (e.g., by binding to a receptor), to reduce the activity of a membrane bound receptor by competing with it for free ligand (e.g., soluble TNF receptors used in reducing inflammation), or to bring about a desired response (e.g., blood vessel growth inhibition, enhancement of the immune response to proliferative cells or tissues).

[0375] Similarly, antibodies directed to a polypeptide of the present invention can also be used to treat disease (as described *supra*, and elsewhere herein). For example, administration of an antibody directed to a polypeptide of the present invention can bind, and/or neutralize the polypeptide, and/or reduce overproduction of the polypeptide. Similarly, administration of an antibody can activate the polypeptide, such as by binding to a polypeptide bound to a membrane (receptor).

[0376] At the very least, the polypeptides of the present invention can be used as molecular weight markers on SDS-PAGE gels or on molecular sieve gel filtration columns using methods well known to those of skill in the art. Polypeptides can also be used to raise antibodies, which in turn are used to measure protein expression from a recombinant cell, as a way of assessing transformation of the host cell. Moreover, the polypeptides of the present invention can be used to test the biological activities described herein.

Diagnostic Asssays

[0377] The compounds of the present invention are useful for diagnosis, treatment, prevention and/or prognosis of various immune/hematopoietic related disorders in mammals, preferably humans. Such disorders include, but are not limited to such as anemias, autoimmune diseases, immunodeficiencies, allergies, asthma, and inflammation) and infectious/parasitic diseases. In preferred embodiments, polynucleotides expressed in

a particular tissue type (see, e.g., Table 1A, column 7) are used to diagnose, detect, prevent, treat and/or prognose disorders associated with the tissue type.

[0378] Immune/hematopoietic antigens are expressed hematopoietic tissues (e.g., bone marrow, fetal liver, and fetal spleen) or cells and tissues of the immune system (e.g., lymph nodes, spleen, B cells, T cells, monocytes, macrophages, dendritic cells, neutrophils, mast cells, basophils, and eosinophils). For a number of immune/hematopoietic-related disorders, substantially altered (increased or decreased) levels of immune/hematopoietic antigen gene expression can be detected in immune/hematopoietic tissue or other cells or bodily fluids (e.g., sera, plasma, urine, semen, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to a "standard" immune/hematopoietic antigen gene expression level, that is, the immune/hematopoietic antigen expression level in immune/hematopoietic tissues or bodily fluids from an individual not having the immune/hematopoietic-related disorder. Thus, the invention provides a diagnostic method useful during diagnosis of an immune/hematopoietic-related disorder, which involves measuring the expression level of the gene encoding the immune/hematopoietic associated polypeptide in immune/hematopoietic tissue or other cells or body fluid from an individual and comparing the measured gene expression level with a standard immune/hematopoietic antigens gene expression level, whereby an increase or decrease in the gene expression level(s) compared to the standard is indicative of an immune/hematopoietic-related disorder.

[0379] In specific embodiments, the invention provides a diagnostic method useful during diagnosis of a disorder of a normal or diseased tissue/cell source corresponding to column 7 of Table 1A, which involves measuring the expression level of the coding sequence of a polynucleotide sequence associated with this tissue/cell source as disclosed in Table 1A in the tissue/cell source or other cells or body fluid from an individual and comparing the expression level of the coding sequence with a standard expression level of the coding sequence of a polynucleotide sequence, whereby an increase or decrease in the gene expression level(s) compared to the standard is indicative of a disorder of a normal or diseased tissue/cell source corresponding to column 7 of Table 1A.

[0380] In particular, it is believed that certain tissues in mammals with cancer of cells of hematopoietic origin or cancer of tissues of the immune system (e.g., lymph nodes, spleen.

bone marrow) express significantly enhanced or reduced levels of normal or altered immune/hematopoietic antigen expression and mRNA encoding the immune/hematopoietic associated polypeptide when compared to a corresponding "standard" level. Further, it is believed that enhanced or depressed levels of the immune/hematopoietic associated polypeptide can be detected in certain body fluids (e.g., sera, plasma, urine, and spinal fluid) or cells or tissue from mammals with such a cancer when compared to sera from mammals of the same species not having the cancer.

[0381] For example, as disclosed herein, immune/hematopoietic associated polypeptides of the invention are expressed in hematopoietic tissues (e.g., bone marrow, fetal liver, and fetal spleen) or cells and tissues of the immune system (e.g., lymph nodes, spleen, B cells, T cells, monocytes, macrophages, dendritic cells, neutrophils, mast cells, basophils, and eosinophils). Accordingly, polynucleotides of the invention (e.g., polynucleotide sequences complementary to all or a portion of an immune/hematopoietic antigen mRNA nucleotide sequence of SEQ ID NO:X, nucleotide sequence encoding SEQ ID NO:Y, nucleotide sequence encoding a polypeptide encoded by SEQ ID NO:X and/or a nucleotide sequence delineated by columns 8 and 9 of Table 2) and antibodies (and antibody fragments) directed against the polypeptides of the invention may be used to quantitate or qualitate concentrations of cells expressing immune/hematopoietic antigens, preferably on their cell surfaces. These polynucleotides and antibodies additionally have diagnostic applications in detecting abnormalities in the level of immune/hematopoietic antigens gene expression, or abnormalities in the structure and/or temporal, tissue, cellular, or subcellular location of immune/hematopoietic antigens. These diagnostic assays may be performed *in vivo* or *in vitro*, such as, for example, on blood samples, biopsy tissue or autopsy tissue. In specific embodiments, polynucleotides and antibodies of the invention are used to quantitate or qualitate tissues/cells corresponding to the library source disclosed in column 7 of Table 1A expressing the corresponding immune/hematopoietic sequence disclosed in the same row of Table 1A, preferrably on their cell surface.

[0382] Thus, the invention provides a diagnostic method useful during diagnosis of an immune/hematopoietic-related disorder, including cancers, which involves measuring the expression level of the gene encoding the immune/hematopoietic antigen polypeptide in immune/hematopoietic tissue or other cells or body fluid from an individual and

comparing the measured gene expression level with a standard immune/hematopoietic antigen gene expression level, whereby an increase or decrease in the gene expression level compared to the standard is indicative of an immune/hematopoietic-related disorder. In specific embodiments, polynucleotides and antibodies of the invention are used to quantitate or qualitate tissues/cells corresponding to the library source disclosed in column 7 of Table 1A expressing the corresponding immune/hematopoietic sequence disclosed in the same row of Table 1A, preferrably on their cell surface.

[0383] Where a diagnosis of an immune/hematopoietic-related disease or disorder, including diagnosis of a tumor, has already been made according to conventional methods, the present invention is useful as a prognostic indicator, whereby patients exhibiting enhanced or depressed immune/hematopoietic antigen gene expression will experience a worse clinical outcome relative to patients expressing the gene at a level nearer the standard level.

[0384] By "assaying the expression level of the gene encoding the immune/hematopoietic associated polypeptide" is intended qualitatively or quantitatively measuring or estimating the level of the immune/hematopoietic antigen polypeptide or the level of the mRNA encoding the immune/hematopoietic antigen polypeptide in a first biological sample either directly (e.g., by determining or estimating absolute protein level or mRNA level) or relatively (e.g., by comparing to the immune/hematopoietic associated polypeptide level or mRNA level in a second biological sample). Preferably, the immune/hematopoietic antigen polypeptide expression level or mRNA level in the first biological sample is measured or estimated and compared to a standard immune/hematopoietic antigen polypeptide level or mRNA level, the standard being taken from a second biological sample obtained from an individual not having the disorder or being determined by averaging levels from a population of individuals not having an immune/hematopoietic –related disorder. As will be appreciated in the art, once a standard immune/hematopoietic antigen polypeptide level or mRNA level is known, it can be used repeatedly as a standard for comparison.

[0385] By "biological sample" is intended any biological sample obtained from an individual, cell line, tissue culture, or other source containing immune/hematopoietic antigen polypeptides (including portions thereof) or mRNA. As indicated, biological samples include body fluids (such as sera, plasma, urine, synovial fluid and spinal fluid)

which contain cells expressing immune/hematopoietic antigen polypeptides, heamtopoietic cells and tissue, cells and tissues of the immune system , and other tissue sources found to express the full length or fragments thereof of an immune/hematopoietic antigen. Methods for obtaining tissue biopsies and body fluids from mammals are well known in the art. Where the biological sample is to include mRNA, a tissue biopsy is the preferred source.

[0386] Total cellular RNA can be isolated from a biological sample using any suitable technique such as the single-step guanidinium-thiocyanate-phenol-chloroform method described in Chomczynski and Sacchi, Anal. Biochem. 162:156-159 (1987). Levels of mRNA encoding the immune/hematopoietic antigen polypeptides are then assayed using any appropriate method. These include Northern blot analysis, S1 nuclease mapping, the polymerase chain reaction (PCR), reverse transcription in combination with the polymerase chain reaction (RT-PCR), and reverse transcription in combination with the ligase chain reaction (RT-LCR).

[0387] The present invention also relates to diagnostic assays such as quantitative and diagnostic assays for detecting levels of immune/hematopoietic antigen polypeptides, in a biological sample (e.g., cells and tissues), including determination of normal and abnormal levels of polypeptides. Thus, for instance, a diagnostic assay in accordance with the invention for detecting over-expression of immune/hematopoietic antigens compared to normal control tissue samples may be used to detect the presence of tumors. Assay techniques that can be used to determine levels of a polypeptide, such as an immune/hematopoietic antigen polypeptide of the present invention in a sample derived from a host are well-known to those of skill in the art. Such assay methods include radioimmunoassays, competitive-binding assays, Western Blot analysis and ELISA assays. Assaying immune/hematopoietic antigen polypeptide levels in a biological sample can occur using any art-known method.

[0388] Assaying immune/hematopoietic antigen polypeptide levels in a biological sample can occur using antibody-based techniques. For example, immune/hematopoietic antigen polypeptide expression in tissues can be studied with classical immunohistological methods (Jalkanen et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, M., et al., J. Cell . Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for detecting immune/hematopoietic antigen polypeptide gene expression include immunoassays, such

as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase, and radioisotopes, such as iodine (^{125}I, ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^{3}H), indium (^{112}In), and technetium (^{99m}Tc), and fluorescent labels, such as fluorescein and rhodamine, and biotin.

[0389] The tissue or cell type to be analyzed will generally include those which are known, or suspected, to express the immune/hematopoietic antigen gene (such as, for example, cells of the immune system or cancers of cells of hematopoetic origin (e.g., leukemias). The protein isolation methods employed herein may, for example, be such as those described in Harlow and Lane (Harlow, E. and Lane, D., 1988, "Antibodies: A Laboratory Manual", Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York), which is incorporated herein by reference in its entirety. The isolated cells can be derived from cell culture or from a patient. The analysis of cells taken from culture may be a necessary step in the assessment of cells that could be used as part of a cell-based gene therapy technique or, alternatively, to test the effect of compounds on the expression of the immune/hematopoietic antigen gene.

[0390] For example, antibodies, or fragments of antibodies, such as those described herein, may be used to quantitatively or qualitatively detect the presence of immune/hematopoietic antigen gene products or conserved variants or peptide fragments thereof. This can be accomplished, for example, by immunofluorescence techniques employing a fluorescently labeled antibody coupled with light microscopic, flow cytometric, or fluorimetric detection.

[0391] In a preferred embodiment, antibodies, or fragments of antibodies directed to any one or all of the predicted epitope domains of the immune/hematopoietic antigen polypeptides (Shown in Table 1A, column 6) may be used to quantitatively or qualitatively detect the presence of immune/hematopoietic antigen gene products or conserved variants or peptide fragments thereof. This can be accomplished, for example, by immunofluorescence techniques employing a fluorescently labeled antibody coupled with light microscopic, flow cytometric, or fluorimetric detection.

[0392] In an additional preferred embodiment, antibodies, or fragments of antibodies directed to a conformational epitope of an immune/hematopoietic antigen may be used to quantitatively or qualitatively detect the presence of immune/hematopoietic antigen gene

products or conserved variants or peptide fragments thereof. This can be accomplished, for example, by immunofluorescence techniques employing a fluorescently labeled antibody coupled with light microscopic, flow cytometric, or fluorimetric detection.

[0393] The antibodies (or fragments thereof), and/or immune/hematopoietic antigen polypeptides of the present invention may, additionally, be employed histologically, as in immunofluorescence, immunoelectron microscopy or non-immunological assays, for in situ detection of immune/hematopoietic antigen gene products or conserved variants or peptide fragments thereof. In situ detection may be accomplished by removing a histological specimen from a patient, and applying thereto a labeled antibody or immune/hematopoietic antigen polypeptide of the present invention. The antibody (or fragment thereof) or immune/hematopoietic antigen polypeptide is preferably applied by overlaying the labeled antibody (or fragment) onto a biological sample. Through the use of such a procedure, it is possible to determine not only the presence of the immune/hematopoietic antigen gene product, or conserved variants or peptide fragments, or immune/hematopoietic antigen polypeptide binding, but also its distribution in the examined tissue. Using the present invention, those of ordinary skill will readily perceive that any of a wide variety of histological methods (such as staining procedures) can be modified in order to achieve such in situ detection.

[0394] Immunoassays and non-immunoassays for immune/hematopoietic antigen gene products or conserved variants or peptide fragments thereof will typically comprise incubating a sample, such as a biological fluid, a tissue extract, freshly harvested cells, or lysates of cells which have been incubated in cell culture, in the presence of a detectably labeled antibody capable of binding immune/hematopoietic antigen gene products or conserved variants or peptide fragments thereof, and detecting the bound antibody by any of a number of techniques well-known in the art.

[0395] The biological sample may be brought in contact with and immobilized onto a solid phase support or carrier such as nitrocellulose, or other solid support which is capable of immobilizing cells, cell particles or soluble proteins. The support may then be washed with suitable buffers followed by treatment with the detectably labeled anti-immune/hematopoietic antigen antibody or detectable immune/hematopoietic antigen polypeptide. The solid phase support may then be washed with the buffer a second time to remove unbound antibody or polypeptide. Optionally the antibody is subsequently

labeled. The amount of bound label on solid support may then be detected by conventional means.

[0396] By "solid phase support or carrier" is intended any support capable of binding an antigen or an antibody. Well-known supports or carriers include glass, polystyrene, polypropylene, polyethylene, dextran, nylon, amylases, natural and modified celluloses, polyacrylamides, gabbros, and magnetite. The nature of the carrier can be either soluble to some extent or insoluble for the purposes of the present invention. The support material may have virtually any possible structural configuration so long as the coupled molecule is capable of binding to an antigen or antibody. Thus, the support configuration may be spherical, as in a bead, or cylindrical, as in the inside surface of a test tube, or the external surface of a rod. Alternatively, the surface may be flat such as a sheet, test strip, etc. Preferred supports include polystyrene beads. Those skilled in the art will know many other suitable carriers for binding antibody or antigen, or will be able to ascertain the same by use of routine experimentation.

[0397] The binding activity of a given lot of anti- immune/hematopoietic antigen antibody or immune/hematopoietic antigen polypeptide may be determined according to well known methods. Those skilled in the art will be able to determine operative and optimal assay conditions for each determination by employing routine experimentation.

[0398] In addition to assaying immune/hematopoietic antigen polypeptide levels or polynucleotide levels in a biological sample obtained from an individual, immune/hematopoietic antigen polypeptide or polynucleotide can also be detected *in vivo* by imaging. For example, in one embodiment of the invention, immune/hematopoietic antigen polypeptide and/or anti-immune/hematopoietic antigen antibodies are used to image immune system diseased cells or diseased hematopoietic cells, such as neoplasms. In another embodiment, immune/hematopoietic antigen polynucleotides of the invention (e.g., polynucleotides complementary to all or a portion of immune/hematopoietic antigen mRNA) and/or anti-immune/hematopoietic antigen antibodies (e.g., antibodies directed to any one or a combination of the epitopes of immune/hematopoietic antigens, antibodies directed to a conformational epitope of immune/hematopoietic antigens, antibodies directed to the full length polypeptide expressed on the cell surface of a mammalian cell) are used to image diseased or neoplastic cells of the immune system or disease or neopalstic cells assoctiated with hematopoiesis.

[0399] Antibody labels or markers for *in vivo* imaging of immune/hematopoietic antigen polypeptides include those detectable by X-radiography, NMR, MRI, CAT-scans or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be incorporated into the antibody by labeling of nutrients for the relevant hybridoma. Where *in vivo* imaging is used to detect enhanced levels of immune/hematopoietic antigen polypeptides for diagnosis in humans, it may be preferable to use human antibodies or "humanized" chimeric monoclonal antibodies. Such antibodies can be produced using techniques described herein or otherwise known in the art. For example methods for producing chimeric antibodies are known in the art. See, for review, Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boulianne et al., Nature 312:643 (1984); Neuberger et al., Nature 314:268 (1985).

[0400] Additionally, any immune/hematopoietic antigen polypeptides whose presence can be detected, can be administered. For example, immune/hematopoietic antigen polypeptides labeled with a radio-opaque or other appropriate compound can be administered and visualized *in vivo*, as discussed, above for labeled antibodies. Further such immune/hematopoietic antigen polypeptides can be utilized for *in vitro* diagnostic procedures.

[0401] An immune/hematopoietic antigen polypeptide-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example, ^{131}I, ^{112}In, ^{99m}Tc), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (for example, parenterally, subcutaneously or intraperitoneally) into the mammal to be examined for an immune/hematopoietic-related disorder. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of ^{99m}Tc. The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain immune/hematopoietic antigen protein.

In vivo tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments" (Chapter 13 in *Tumor Imaging: The Radiochemical Detection of Cancer*, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982)).

[0402] With respect to antibodies, one of the ways in which the anti-immune/hematopoietic antigen antibody can be detectably labeled is by linking the same to an enzyme and using the linked product in an enzyme immunoassay (EIA) (Voller, A., "The Enzyme Linked Immunosorbent Assay (ELISA)", 1978, Diagnostic Horizons 2:1-7, Microbiological Associates Quarterly Publication, Walkersville, MD); Voller et al., J. Clin. Pathol. 31:507-520 (1978); Butler, J.E., Meth. Enzymol. 73:482-523 (1981); Maggio, E. (ed.), 1980, Enzyme Immunoassay, CRC Press, Boca Raton, FL,; Ishikawa, E. et al., (eds.), 1981, Enzyme Immunoassay, Kgaku Shoin, Tokyo). The enzyme which is bound to the antibody will react with an appropriate substrate, preferably a chromogenic substrate, in such a manner as to produce a chemical moiety which can be detected, for example, by spectrophotometric, fluorimetric or by visual means. Enzymes which can be used to detectably label the antibody include, but are not limited to, malate dehydrogenase, staphylococcal nuclease, delta-5-steroid isomerase, yeast alcohol dehydrogenase, alpha-glycerophosphate, dehydrogenase, triose phosphate isomerase, horseradish peroxidase, alkaline phosphatase, asparaginase, glucose oxidase, beta-galactosidase, ribonuclease, urease, catalase, glucose-6-phosphate dehydrogenase, glucoamylase and acetylcholinesterase. Additionally, the detection can be accomplished by colorimetric methods which employ a chromogenic substrate for the enzyme. Detection may also be accomplished by visual comparison of the extent of enzymatic reaction of a substrate in comparison with similarly prepared standards.

[0403] Detection may also be accomplished using any of a variety of other immunoassays. For example, by radioactively labeling the antibodies or antibody fragments, it is possible to detect immune/hematopoietic antigens through the use of a radioimmunoassay (RIA) (see, for example, Weintraub, B., Principles of Radioimmunoassays, Seventh Training Course on Radioligand Assay Techniques, The Endocrine Society, March, 1986, which is incorporated by reference herein). The radioactive isotope can be detected by means including, but not limited to, a gamma counter, a scintillation counter, or autoradiography.

[0404] It is also possible to label the antibody with a fluorescent compound. When the fluorescently labeled antibody is exposed to light of the proper wave length, its presence can then be detected due to fluorescence. Among the most commonly used fluorescent labeling compounds are fluorescein isothiocyanate, rhodamine, phycoerythrin, phycocyanin, allophycocyanin, ophthaldehyde and fluorescamine.

[0405] The antibody can also be detectably labeled using fluorescence emitting metals such as ^{152}Eu, or others of the lanthanide series. These metals can be attached to the antibody using such metal chelating groups as diethylenetriaminepentacetic acid (DTPA) or ethylenediaminetetraacetic acid (EDTA).

[0406] The antibody also can be detectably labeled by coupling it to a chemiluminescent compound. The presence of the chemiluminescent-tagged antibody is then determined by detecting the presence of luminescence that arises during the course of a chemical reaction. Examples of particularly useful chemiluminescent labeling compounds are luminol, isoluminol, theromatic acridinium ester, imidazole, acridinium salt and oxalate ester.

[0407] Likewise, a bioluminescent compound may be used to label the antibody of the present invention. Bioluminescence is a type of chemiluminescence found in biological systems in, which a catalytic protein increases the efficiency of the chemiluminescent reaction. The presence of a bioluminescent protein is determined by detecting the presence of luminescence. Important bioluminescent compounds for purposes of labeling are luciferin, luciferase and aequorin.

Methods for Detecting Immune/Hematopoietic-Related Disease, Including Cancer

[0408] In general, an immune/hematopoietic-related disease or cancer may be detected in a patient based on the presence of one or more immune/hematopoietic antigen proteins of the invention and/or polynucleotides encoding such proteins in a biological sample (for example, blood, sera, urine, and/or tumor biopsies) obtained from the patient. In other words, such proteins and/or polynucleotides may be used as markers to indicate the presence or absence of an immune/hematopoietic-related disease or disorder, including cancer. Cancers that may be diagnosed, and/or prognosed using the compositions of the invention include but are not limited to, cancers of cells of hematopoietic origins such as leukemias and lymphomas. In addition, such proteins and/or polynucleotids may be useful

for the detection of other diseases and cancers, including cancers of tissues/cells corresponding to the library source disclosed in column 7 of Table 1A expressing the corresponding immune/hematopoietic sequence disclosed in the same row of Table 1A. The binding agents provided herein generally permit detection of the level of antigen that binds to the agent in the biological sample. Polynucleotide primers and probes may be used to detect the level of mRNA encoding immune/hematopoietic antigen polypeptides, which is also indicative of the presence or absence of an immune/hematopoietic-related disease or disorder, including cancer. In general, immune/hematopoietic antigen polypeptides should be present at a level that is at least three fold higher in diseased tissue than in normal tissue.

[0409] There are a variety of assay formats known to those of ordinary skill in the art for using a binding agent to detect polypeptide markers in a sample. See, e.g., Harlow and Lane, *supra*. In general, the presence or absence of an immune/hematopoietic-related disease in a patient may be determined by (a) contacting a biological sample obtained from a patient with a binding agent; (b) detecting in the sample a level of polypeptide that binds to the binding agent; and (c) comparing the level of polypeptide with a predetermined cut-off value.

[0410] In a preferred embodiment, the assay involves the use of binding agent immobilized on a solid support to bind to and remove the immune/hematopoietic antigen polypeptide of the invention from the remainder of the sample. The bound polypeptide may then be detected using a detection reagent that contains a reporter group and specifically binds to the binding agent/polypeptide complex. Such detection reagents may comprise, for example, a binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an anti-immunoglobulin, protein G, protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding agent after incubation of the binding agent with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding agent is indicative of the reactivity of the sample with the immobilized binding agent. Suitable polypeptides for use within such assays include immune/hematopoietic antigen polypeptides and portions thereof, or antibodies, to which the binding agent binds, as described above.

[0411] The solid support may be any material known to those of skill in the art to which immune/hematopoietic antigen polypeptides of the invention may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the agent and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for the suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10 ug, and preferably about 100 ng to about 1 ug, is sufficient to immobilize an adequate amount of binding agent.

[0412] Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (see, e.g., Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

Gene Therapy Methods

[0413] Also encompassed by the present invention are gene therapy methods for treating or preventing disorders, diseases and conditions. The gene therapy methods relate to the introduction of nucleic acid (DNA, RNA and antisense DNA or RNA) sequences into an animal to achieve expression of an immune/hematopoietic antigen of the present

invention. This method requires a polynucleotide which codes for a polypeptide of the present invention operatively linked to a promoter and any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques are known in the art, see, for example, WO90/11092, which is herein incorporated by reference.

[0414] Thus, for example, cells from a patient may be engineered with a polynucleotide (DNA or RNA) comprising a promoter operably linked to a polynucleotide of the present invention ex vivo, with the engineered cells then being provided to a patient to be treated with the polypeptide of the present invention. Such methods are well-known in the art. For example, see Belldegrun, A., et al., J. Natl. Cancer Inst. 85: 207-216 (1993); Ferrantini, M. et al., Cancer Research 53: 1107-1112 (1993); Ferrantini, M. et al., J. Immunology 153: 4604-4615 (1994); Kaido, T., et al., Int. J. Cancer 60: 221-229 (1995); Ogura, H., et al., Cancer Research 50: 5102-5106 (1990); Santodonato, L., et al., Human Gene Therapy 7:1-10 (1996); Santodonato, L., et al., Gene Therapy 4:1246-1255 (1997); and Zhang, J.-F. et al., Cancer Gene Therapy 3: 31-38 (1996)), which are herein incorporated by reference. In one embodiment, the cells which are engineered are arterial cells. The arterial cells may be reintroduced into the patient through direct injection to the artery, the tissues surrounding the artery, or through catheter injection.

[0415] As discussed in more detail below, the polynucleotide constructs can be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, and the like). The polynucleotide constructs may be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

[0416] In one embodiment, the polynucleotide of the present invention is delivered as a naked polynucleotide. The term "naked" polynucleotide, DNA or RNA refers to sequences that are free from any delivery vehicle that acts to assist, promote or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotide of the present invention can also be delivered in liposome formulations and lipofectin formulations and the like can be prepared by methods well known to those skilled in the art. Such methods are described, for example, in U.S. Patent Nos. 5,593,972, 5,589,466, and 5,580,859, which are herein incorporated by reference.

[0417] The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Appropriate vectors include pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; pSVK3, pBPV, pMSG and pSVL available from Pharmacia; and pEF1/V5, pcDNA3.1, and pRc/CMV2 available from Invitrogen. Other suitable vectors will be readily apparent to the skilled artisan.

[0418] Any strong promoter known to those skilled in the art can be used for driving the expression of the polynucleotide sequence. Suitable promoters include adenoviral promoters, such as the adenoviral major late promoter; or heterologous promoters, such as the cytomegalovirus (CMV) promoter; the respiratory syncytial virus (RSV) promoter; inducible promoters, such as the MMT promoter, the metallothionein promoter; heat shock promoters; the albumin promoter; the ApoAI promoter; human globin promoters; viral thymidine kinase promoters, such as the Herpes Simplex thymidine kinase promoter; retroviral LTRs; the b-actin promoter; and human growth hormone promoters. The promoter also may be the native promoter for the polynucleotide of the present invention.

[0419] Unlike other gene therapy techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

[0420] The polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular, fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are

differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

[0421] For the naked nucleic acid sequence injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 mg/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration.

[0422] The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked DNA constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

[0423] The naked polynucleotides are delivered by any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, and so-called "gene guns". These delivery methods are known in the art.

[0424] The constructs may also be delivered with delivery vehicles such as viral sequences, viral particles, liposome formulations, lipofectin, precipitating agents, etc. Such methods of delivery are known in the art.

[0425] In certain embodiments, the polynucleotide constructs are complexed in a liposome preparation. Liposomal preparations for use in the instant invention include cationic (positively charged), anionic (negatively charged) and neutral preparations. However, cationic liposomes are particularly preferred because a tight charge complex can be formed between the cationic liposome and the polyanionic nucleic acid. Cationic liposomes have been shown to mediate intracellular delivery of plasmid DNA (Felgner et al., Proc. Natl. Acad. Sci. USA (1987) 84:7413-7416, which is herein incorporated by reference); mRNA (Malone et al., Proc. Natl. Acad. Sci. USA (1989) 86:6077-6081,

which is herein incorporated by reference); and purified transcription factors (Debs et al., J. Biol. Chem. (1990) 265:10189-10192, which is herein incorporated by reference), in functional form.

[0426] Cationic liposomes are readily available. For example, N[1-2,3-dioleyloxy)propyl]-N,N,N-triethylammonium (DOTMA) liposomes are particularly useful and are available under the trademark Lipofectin, from GIBCO BRL, Grand Island, N.Y., (see, also, Felgner et al., Proc. Natl Acad. Sci. USA (1987) 84:7413-7416, which is herein incorporated by reference). Other commercially available liposomes include transfectace (DDAB/DOPE) and DOTAP/DOPE (Boehringer).

[0427] Other cationic liposomes can be prepared from readily available materials using techniques well known in the art. See, e.g. PCT Publication No. WO 90/11092 (which is herein incorporated by reference) for a description of the synthesis of DOTAP (1,2-bis(oleoyloxy)-3-(trimethylammonio)propane) liposomes. Preparation of DOTMA liposomes is explained in the literature, see, e.g., P. Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417, which is herein incorporated by reference. Similar methods can be used to prepare liposomes from other cationic lipid materials.

[0428] Similarly, anionic and neutral liposomes are readily available, such as from Avanti Polar Lipids (Birmingham, Ala.), or can be easily prepared using readily available materials. Such materials include phosphatidyl choline, cholesterol, phosphatidyl ethanolamine, dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), dioleoylphoshatidyl ethanolamine (DOPE), among others. These materials can also be mixed with the DOTMA and DOTAP starting materials in appropriate ratios. Methods for making liposomes using these materials are well known in the art.

[0429] For example, commercially dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), and dioleoylphosphatidyl ethanolamine (DOPE) can be used in various combinations to make conventional liposomes, with or without the addition of cholesterol. Thus, for example, DOPG/DOPC vesicles can be prepared by drying 50 mg each of DOPG and DOPC under a stream of nitrogen gas into a sonication vial. The sample is placed under a vacuum pump overnight and is hydrated the following day with deionized water. The sample is then sonicated for 2 hours in a capped vial, using a Heat Systems model 350 sonicator equipped with an inverted cup (bath type) probe at the maximum setting while the bath is circulated at 15EC. Alternatively, negatively

charged vesicles can be prepared without sonication to produce multilamellar vesicles or by extrusion through nucleopore membranes to produce unilamellar vesicles of discrete size. Other methods are known and available to those of skill in the art.

[0430] The liposomes can comprise multilamellar vesicles (MLVs), small unilamellar vesicles (SUVs), or large unilamellar vesicles (LUVs), with SUVs being preferred. The various liposome-nucleic acid complexes are prepared using methods well known in the art. See, e.g., Straubinger et al., Methods of Immunology (1983), 101:512-527, which is herein incorporated by reference. For example, MLVs containing nucleic acid can be prepared by depositing a thin film of phospholipid on the walls of a glass tube and subsequently hydrating with a solution of the material to be encapsulated. SUVs are prepared by extended sonication of MLVs to produce a homogeneous population of unilamellar liposomes. The material to be entrapped is added to a suspension of preformed MLVs and then sonicated. When using liposomes containing cationic lipids, the dried lipid film is resuspended in an appropriate solution such as sterile water or an isotonic buffer solution such as 10 mM Tris/NaCl, sonicated, and then the preformed liposomes are mixed directly with the DNA. The liposome and DNA form a very stable complex due to binding of the positively charged liposomes to the cationic DNA. SUVs find use with small nucleic acid fragments. LUVs are prepared by a number of methods, well known in the art. Commonly used methods include Ca^{2+}-EDTA chelation (Papahadjopoulos et al., Biochim. Biophys. Acta (1975) 394:483; Wilson et al., Cell 17:77 (1979); ether injection (Deamer, D. and Bangham, A., Biochim. Biophys. Acta 443:629 (1976); Ostro et al., Biochem. Biophys. Res. Commun. 76:836 (1977); Fraley et al., Proc. Natl. Acad. Sci. USA 76:3348 (1979)); detergent dialysis (Enoch, H. and Strittmatter, P., Proc. Natl. Acad. Sci. USA 76:145 (1979)); and reverse-phase evaporation (REV) (Fraley et al., J. Biol. Chem. 255:10431 (1980); Szoka et al., Proc. Natl. Acad. Sci. USA 75:145 (1978); Schaefer-Ridder et al., Science 215:166 (1982)), which are herein incorporated by reference.

[0431] Generally, the ratio of DNA to liposomes will be from about 10:1 to about 1:10. Preferably, the ration will be from about 5:1 to about 1:5. More preferably, the ration will be about 3:1 to about 1:3. Still more preferably, the ratio will be about 1:1.

[0432] U.S. Patent No. 5,676,954 (which is herein incorporated by reference) reports on the injection of genetic material, complexed with cationic liposomes carriers, into mice. U.S.

Patent Nos. 4,897,355, 4,946,787, 5,049,386, 5,459,127, 5,589,466, 5,693,622, 5,580,859, 5,703,055, and international publication no. WO 94/9469 (which are herein incorporated by reference) provide cationic lipids for use in transfecting DNA into cells and mammals. U.S. Patent Nos. 5,589,466, 5,693,622, 5,580,859, 5,703,055, and International Publication No. WO 94/9469 provide methods for delivering DNA-cationic lipid complexes to mammals.

[0433] In certain embodiments, cells are engineered, ex vivo or *in vivo*, using a retroviral particle containing RNA which comprises a sequence encoding a polypeptide of the present invention. Retroviruses from which the retroviral plasmid vectors may be derived include, but are not limited to, Moloney Murine Leukemia Virus, spleen necrosis virus, Rous sarcoma Virus, Harvey Sarcoma Virus, avian leukosis virus, gibbon ape leukemia virus, human immunodeficiency virus, Myeloproliferative Sarcoma Virus, and mammary tumor virus.

[0434] The retroviral plasmid vector is employed to transduce packaging cell lines to form producer cell lines. Examples of packaging cells which may be transfected include, but are not limited to, the PE501, PA317, R-2, R-AM, PA12, T19-14X, VT-19-17-H2, RCRE, RCRIP, GP+E-86, GP+envAm12, and DAN cell lines as described in Miller, Human Gene Therapy 1:5-14 (1990), which is incorporated herein by reference in its entirety. The vector may transduce the packaging cells through any means known in the art. Such means include, but are not limited to, electroporation, the use of liposomes, and $CaPO_4$ precipitation. In one alternative, the retroviral plasmid vector may be encapsulated into a liposome, or coupled to a lipid, and then administered to a host.

[0435] The producer cell line generates infectious retroviral vector particles which include polynucleotide encoding a polypeptide of the present invention. Such retroviral vector particles then may be employed, to transduce eukaryotic cells, either *in vitro* or *in vivo*. The transduced eukaryotic cells will express a polypeptide of the present invention.

[0436] In certain other embodiments, cells are engineered, ex vivo or *in vivo*, with polynucleotide contained in an adenovirus vector. Adenovirus can be manipulated such that it encodes and expresses a polypeptide of the present invention, and at the same time is inactivated in terms of its ability to replicate in a normal lytic viral life cycle. Adenovirus expression is achieved without integration of the viral DNA into the host cell chromosome, thereby alleviating concerns about insertional mutagenesis. Furthermore,

adenoviruses have been used as live enteric vaccines for many years with an excellent safety profile (Schwartz, et al., Am. Rev. Respir. Dis.109:233-238 (1974)). Finally, adenovirus mediated gene transfer has been demonstrated in a number of instances including transfer of alpha-1-antitrypsin and CFTR to the lungs of cotton rats (Rosenfeld et al., Science 252:431-434 (1991); Rosenfeld et al., Cell 68:143-155 (1991)). Furthermore, extensive studies to attempt to establish adenovirus as a causative agent in human cancer were uniformly negative (Green et al., Proc. Natl. Acad. Sci. USA 76:6606 (1979)).

[0437] Suitable adenoviral vectors useful in the present invention are described, for example, in Kozarsky and Wilson, Curr. Opin. Genet. Devel. 3:499-503 (1993); Rosenfeld et al., Cell 68:143-155 (1992); Engelhardt et al., Human Genet. Ther. 4:759-769 (1993); Yang et al., Nature Genet. 7:362-369 (1994); Wilson et al., Nature 365:691-692 (1993); and U.S. Patent No. 5,652,224, which are herein incorporated by reference. For example, the adenovirus vector Ad2 is useful and can be grown in human 293 cells. These cells contain the E1 region of adenovirus and constitutively express Ela and Elb, which complement the defective adenoviruses by providing the products of the genes deleted from the vector. In addition to Ad2, other varieties of adenovirus (e.g., Ad3, Ad5, and Ad7) are also useful in the present invention.

[0438] Preferably, the adenoviruses used in the present invention are replication deficient. Replication deficient adenoviruses require the aid of a helper virus and/or packaging cell line to form infectious particles. The resulting virus is capable of infecting cells and can express a polynucleotide of interest which is operably linked to a promoter, but cannot replicate in most cells. Replication deficient adenoviruses may be deleted in one or more of all or a portion of the following genes: E1a, E1b, E3, E4, E2a, or L1 through L5.

[0439] In certain other embodiments, the cells are engineered, ex vivo or *in vivo*, using an adeno-associated virus (AAV). AAVs are naturally occurring defective viruses that require helper viruses to produce infectious particles (Muzyczka, N., Curr. Topics in Microbiol. Immunol. 158:97 (1992)). It is also one of the few viruses that may integrate its DNA into non-dividing cells. Vectors containing as little as 300 base pairs of AAV can be packaged and can integrate, but space for exogenous DNA is limited to about 4.5 kb. Methods for producing and using such AAVs are known in the art. See, for example, U.S.

Patent Nos. 5,139,941, 5,173,414, 5,354,678, 5,436,146, 5,474,935, 5,478,745, and 5,589,377.

[0440] For example, an appropriate AAV vector for use in the present invention will include all the sequences necessary for DNA replication, encapsidation, and host-cell integration. The polynucleotide construct is inserted into the AAV vector using standard cloning methods, such as those found in Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press (1989). The recombinant AAV vector is then transfected into packaging cells which are infected with a helper virus, using any standard technique, including lipofection, electroporation, calcium phosphate precipitation, etc. Appropriate helper viruses include adenoviruses, cytomegaloviruses, vaccinia viruses, or herpes viruses. Once the packaging cells are transfected and infected, they will produce infectious AAV viral particles which contain the polynucleotide construct. These viral particles are then used to transduce eukaryotic cells, either ex vivo or *in vivo*. The transduced cells will contain the polynucleotide construct integrated into its genome, and will express a polypeptide of the invention.

[0441] Another method of gene therapy involves operably associating heterologous control regions and endogenous immune/hematopoietic antigen polynucleotide sequences (e.g., encoding an immune/hematopoietic antigen polypeptide of the present invention) via homologous recombination (see, e.g., U.S. Patent No. 5,641,670, issued June 24, 1997; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al., Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature 342:435-438 (1989), which are herein incorporated by reference. This method involves the activation of a gene which is present in the target cells, but which is not normally expressed in the cells, or is expressed at a lower level than desired.

[0442] Polynucleotide constructs are made, using standard techniques known in the art, which contain the promoter with targeting sequences flanking the promoter. Suitable promoters are described herein. The targeting sequence is sufficiently complementary to an endogenous sequence to permit homologous recombination of the promoter-targeting sequence with the endogenous sequence. The targeting sequence will be sufficiently near the 5' end of the desired endogenous polynucleotide sequence so the promoter will be operably linked to the endogenous sequence upon homologous recombination.

[0443] The promoter and the targeting sequences can be amplified using PCR. Preferably, the amplified promoter contains distinct restriction enzyme sites on the 5' and 3' ends. Preferably, the 3' end of the first targeting sequence contains the same restriction enzyme site as the 5' end of the amplified promoter and the 5' end of the second targeting sequence contains the same restriction site as the 3' end of the amplified promoter. The amplified promoter and targeting sequences are digested and ligated together.

[0444] The promoter-targeting sequence construct is delivered to the cells, either as naked polynucleotide, or in conjunction with transfection-facilitating agents, such as liposomes, viral sequences, viral particles, whole viruses, lipofection, precipitating agents, etc., described in more detail above. The P promoter-targeting sequence can be delivered by any method, included direct needle injection, intravenous injection, topical administration, catheter infusion, particle accelerators, etc. The methods are described in more detail below.

[0445] The promoter-targeting sequence construct is taken up by cells. Homologous recombination between the construct and the endogenous sequence takes place, such that an endogenous sequence is placed under the control of the promoter. The promoter then drives the expression of the endogenous sequence.

[0446] The polynucleotide encoding a polypeptide of the present invention may contain a secretory signal sequence that facilitates secretion of the protein. Typically, the signal sequence is positioned in the coding region of the polynucleotide to be expressed towards or at the 5' end of the coding region. The signal sequence may be homologous or heterologous to the immune/hematopoietic antigen polynucleotide of interest and may be homologous or heterologous to the cells to be transfected. Additionally, the signal sequence may be chemically synthesized using methods known in the art.

[0447] Any mode of administration of any of the above-described polynucleotides constructs can be used so long as the mode results in the expression of one or more molecules in an amount sufficient to provide a therapeutic effect. This includes direct needle injection, systemic injection, catheter infusion, biolistic injectors, particle accelerators (i.e., "gene guns"), gelfoam sponge depots, other commercially available depot materials, osmotic pumps (e.g., Alza minipumps), oral or suppositorial solid (tablet or pill) pharmaceutical formulations, and decanting or topical applications during surgery. For example, direct injection of naked calcium phosphate-precipitated plasmid into rat

liver and rat spleen or a protein-coated plasmid into the portal vein has resulted in gene expression of the foreign gene in the rat livers (Kaneda et al., Science 243:375 (1989)).

[0448] A preferred method of local administration is by direct injection. Preferably, a recombinant molecule of the present invention complexed with a delivery vehicle is administered by direct injection into or locally within the area of arteries. Administration of a composition locally within the area of arteries refers to injecting the composition centimeters and preferably, millimeters within arteries.

[0449] Another method of local administration is to contact a polynucleotide construct of the present invention in or around a surgical wound. For example, a patient can undergo surgery and the polynucleotide construct can be coated on the surface of tissue inside the wound or the construct can be injected into areas of tissue inside the wound.

[0450] Therapeutic compositions useful in systemic administration, include recombinant molecules of the present invention complexed to a targeted delivery vehicle of the present invention. Suitable delivery vehicles for use with systemic administration comprise liposomes comprising ligands for targeting the vehicle to a particular site. In specific embodiments, suitable delivery vehicles for use with systemic administration comprise liposomes comprising polypeptides of the invention for targeting the vehicle to a particular site.

[0451] Preferred methods of systemic administration, include intravenous injection, aerosol, oral and percutaneous (topical) delivery. Intravenous injections can be performed using methods standard in the art. Aerosol delivery can also be performed using methods standard in the art (see, for example, Stribling et al., Proc. Natl. Acad. Sci. USA 189:11277-11281, 1992, which is incorporated herein by reference). Oral delivery can be performed by complexing a polynucleotide construct of the present invention to a carrier capable of withstanding degradation by digestive enzymes in the gut of an animal. Examples of such carriers, include plastic capsules or tablets, such as those known in the art. Topical delivery can be performed by mixing a polynucleotide construct of the present invention with a lipophilic reagent (e.g., DMSO) that is capable of passing into the skin.

[0452] Determining an effective amount of substance to be delivered can depend upon a number of factors including, for example, the chemical structure and biological activity of the substance, the age and weight of the animal, the precise condition requiring treatment and its severity, and the route of administration. The frequency of treatments depends

upon a number of factors, such as the amount of polynucleotide constructs administered per dose, as well as the health and history of the subject. The precise amount, number of doses, and timing of doses will be determined by the attending physician or veterinarian.

[0453] Therapeutic compositions of the present invention can be administered to any animal, preferably to mammals and birds. Preferred mammals include humans, dogs, cats, mice, rats, rabbits sheep, cattle, horses and pigs, with humans being particularly preferred.

Biological Activities

[0454] Polynucleotides or polypeptides, or agonists or antagonists of the present invention, can be used in assays to test for one or more biological activities. If these polynucleotides or polypeptides, or agonists or antagonists of the present invention, do exhibit activity in a particular assay, it is likely that these molecules may be involved in the diseases associated with the biological activity. Thus, the polynucleotides and polypeptides, and agonists or antagonists could be used to treat, prevent diagnose and/or prognose the associated disease.

[0455] The immune/hematopoietic antigen polynucleotides and polypeptides of the invention are predicted to have predominant expression in hematopoietic tissues (e.g., bone marrow, fetal liver, and fetal spleen) or cells and tissues of the immune system (e.g., lymph nodes, spleen, B cells, T cells, monocytes, macrophages, dendritic cells, neutrophils, mast cells, basophils, and eosinophils).

[0456] Thus, the hematopoietic tissues (e.g., bone marrow, fetal liver, and fetal spleen) or cells and tissues of the immune system (e.g., lymph nodes, spleen, B cells, T cells, monocytes, macrophages, dendritic cells, neutrophils, mast cells, basophils, and eosinophils) antigens of the invention may be useful as therapeutic molecules. Each would be useful for diagnosis, detection, treatment and/or prevention of diseases or disorders of the immune system and or diseases and disorders of hematopoiesis, such as anemias, autoimmune diseases, immunodeficiencies, allergies, asthma, and inflammation) and infectious/parasitic diseases.

[0457] In a preferred embodiment, polynucleotides of the invention (e.g., a nucleic acid sequence of SEQ ID NO:X or the complement thereof; or the cDNA sequence contained in Clone ID NO:Z, or fragments or variants thereof) and/or polypeptides of the invention (e.g., an amino acid sequence contained in SEQ ID NO:Y, an amino acid

sequence encoded by SEQ ID NO:X, or the complement threof, an amino acid sequence encoded by the cDNA sequence contained in Clone ID NO:Z and fragments or variants thereof as described herein) are useful for the diagnosis, detection, treatement, and/or prevention of diseases or disorders of the tissues/cells corresponding to the library source disclosed in column 7 of Table 1A expressing the corresponding immune/hematopoietic sequence disclosed in the same row of Table 1A.

[0458] Particularly, the immune/hematopoietic antigens may be a useful therapeutic for cancers of cells of hematopoitic origin. Treatment, diagnosis, detection, and/or prevention of immune/hematopoietic-related disorders could be carried out using an immune/hematopoietic antigen or soluble form of an immune/hematopoietic antigen, an immune/hematopoietic antigen ligand, gene therapy, or ex vivo applications. Moreover, inhibitors of an immune/hematopoietic antigen, either blocking antibodies or mutant forms, could modulate the expression of the immune/hematopoietic antigen. These inhibitors may be useful to treat, diagnose, detect, and/or prevent diseases associated with the misregulation of an immune/hematopoietic antigen.

[0459] In one embodiment, the invention provides a method for the specific delivery of compositions of the invention to cells (e.g., normal or diseased immune/hematopoietic cells) by administering polypeptides of the invention (e.g., immune/hematopoietic antigen polypeptides or anti-immune/hematopoietic antigen antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a therapeutic protein into the targeted cell (e.g., an aberrant immune/hematopoietic cell or immune/hematopoietic cancer cell). In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

[0460] In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of aberrant immune/hematopoietic cells, including, but not limited to, immune/hematopoietic tumor cells) by administering polypeptides of the invention (e.g., immune/hematopoietic antigen polypeptides or fragments thereof, or anti- immune/hematopoietic antigen antibodies) in association with toxins or cytotoxic prodrugs.

[0461] By "toxin" is meant compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, cytotoxins (cytotoxic agents), or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNAse, alpha toxin, ricin, abrin, *Pseudomonas* exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin. "Toxin" also includes a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example, ^{213}Bi, or other radioisotopes such as, for example, ^{103}Pd, ^{133}Xe, ^{131}I, ^{68}Ge, ^{57}Co, ^{65}Zn, ^{85}Sr, ^{32}P, ^{35}S, ^{90}Y, ^{153}Sm, ^{153}Gd, ^{169}Yb, ^{51}Cr, ^{54}Mn, ^{75}Se, ^{113}Sn, ^{90}Yttrium, ^{117}Tin, ^{186}Rhenium, ^{166}Holmium, and ^{188}Rhenium; luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

[0462] Techniques known in the art may be applied to label antibodies of the invention. Such techniques include, but are not limited to, the use of bifunctional conjugating agents (see e.g., U.S. Patent Nos. 5,756,065; 5,714,631; 5,696,239; 5,652,361; 5,505,931; 5,489,425; 5,435,990; 5,428,139; 5,342,604; 5,274,119; 4,994,560; and 5,808,003; the contents of each of which are hereby incorporated by reference in its entirety). A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include paclitaxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclothosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis- dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin,

mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine).

[0463] By "cytotoxic prodrug" is meant a non-toxic compound that is converted by an enzyme, normally present in the cell, into a cytotoxic compound. Cytotoxic prodrugs that may be used according to the methods of the invention include, but are not limited to, glutamyl derivatives of benzoic acid mustard alkylating agent, phosphate derivatives of etoposide or mitomycin C, cytosine arabinoside, daunorubisin, and phenoxyacetamide derivatives of doxorubicin.

[0464] It will be appreciated that conditions caused by a decrease in the standard or normal level of immune/hematopoietic antigen activity in an individual, particularly in individuals with immune/hematopoietic-related disorders, can be treated by administration of an immune/hematopoietic antigen polypeptide (e.g., such as, for example, the complete immune/hematopoietic antigen polypeptide, the soluble form of the extracellular domain of an immune/hematopoietic antigen polypeptide, or cells expressing the complete protein) or agonist. Thus, the invention also provides a method of treatment of an individual in need of an increased level of immune/hematopoietic antigen activity comprising administering to such an individual a pharmaceutical composition comprising an amount of an isolated immune/hematopoietic antigen polypeptide of the invention, or agonist thereof (e.g., an agonistic anti- immune/hematopoietic antigen antibody), effective to increase the immune/hematopoietic antigen activity level in such an individual.

[0465] It will also be appreciated that conditions caused by a increase in the standard or normal level of immune/hematopoietic antigen activity in an individual, particularly in an individual with an immune/hematopoietic-related disorder, can be treated by administration of immune/hematopoietic antigen polypeptides (e.g., such as, for example, the complete immune/hematopoietic antigen polypeptide, the soluble form of the extracellular domain of an immune/hematopoietic antigen polypeptide, or cells expressing the complete protein) or antagonist (e.g., an antagonistic anti-immune/hematopoietic antigen antibody). Thus, the invention also provides a method of treatment of an individual in need of an decreased level of immune/hematopoietic antigen activity comprising administering to such an individual a pharmaceutical composition comprising an amount of an isolated immune/hematopoietic antigen polypeptide of the invention, or antagonist thereof (e.g., an antagonistic anti-immune/hematopoietic antigen antibody),

effective to decrease the immune/hematopoietic antigen activity level in such an individual.

[0466] In certain embodiments, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to diagnose and/or prognose diseases and/or disorders associated with the tissue(s) in which the polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in Table 1A, column 7 (Tissue Distribution Library Code).

[0467] More generally, polynucleotides, translation products and antibodies corresponding to this gene may be useful for the diagnosis, prognosis, prevention, and/or treatment of diseases and/or disorders associated with the following systems.

Immune Activity

[0468] Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, diagnosing and/or prognosing diseases, disorders, and/or conditions of the immune system, by, for example, activating or inhibiting the proliferation, differentiation, or mobilization (chemotaxis) of immune cells. Immune cells develop through a process called hematopoiesis, producing myeloid (platelets, red blood cells, neutrophils, and macrophages) and lymphoid (B and T lymphocytes) cells from pluripotent stem cells. The etiology of these immune diseases, disorders, and/or conditions may be genetic, somatic, such as cancer and some autoimmune diseases, acquired (e.g., by chemotherapy or toxins), or infectious. Moreover, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention can be used as a marker or detector of a particular immune system disease or disorder.

[0469] In another embodiment, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to treat diseases and disorders of the immune system and/or to inhibit or enhance an immune response generated by cells associated with the tissue(s) in which the polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in Table 1A, column 7 (Tissue Distribution Library Code).

[0470] Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, diagnosing, and/or prognosing immunodeficiencies, including both congenital and acquired immunodeficiencies. Examples of B cell immunodeficiencies in which immunoglobulin levels B cell function and/or B cell numbers are decreased include: X-linked agammaglobulinemia (Bruton's disease), X-linked infantile agammaglobulinemia, X-linked immunodeficiency with hyper IgM, non X-linked immunodeficiency with hyper IgM, X-linked lymphoproliferative syndrome (XLP), agammaglobulinemia including congenital and acquired agammaglobulinemia, adult onset agammaglobulinemia, late-onset agammaglobulinemia, dysgammaglobulinemia, hypogammaglobulinemia, unspecified hypogammaglobulinemia, recessive agammaglobulinemia (Swiss type), Selective IgM deficiency, selective IgA deficiency, selective IgG subclass deficiencies, IgG subclass deficiency (with or without IgA deficiency), Ig deficiency with increased IgM, IgG and IgA deficiency with increased IgM, antibody deficiency with normal or elevated Igs, Ig heavy chain deletions, kappa chain deficiency, B cell lymphoproliferative disorder (BLPD), common variable immunodeficiency (CVID), common variable immunodeficiency (CVI) (acquired), and transient hypogammaglobulinemia of infancy.

[0471] In specific embodiments, ataxia-telangiectasia or conditions associated with ataxia-telangiectasia are treated, prevented, diagnosed, and/or prognosing using the polypeptides or polynucleotides of the invention, and/or agonists or antagonists thereof.

[0472] Examples of congenital immunodeficiencies in which T cell and/or B cell function and/or number is decreased include, but are not limited to: DiGeorge anomaly, severe combined immunodeficiencies (SCID) (including, but not limited to, X-linked SCID, autosomal recessive SCID, adenosine deaminase deficiency, purine nucleoside phosphorylase (PNP) deficiency, Class II MHC deficiency (Bare lymphocyte syndrome), Wiskott-Aldrich syndrome, and ataxia telangiectasia), thymic hypoplasia, third and fourth pharyngeal pouch syndrome, 22q11.2 deletion, chronic mucocutaneous candidiasis, natural killer cell deficiency (NK), idiopathic CD4+ T-lymphocytopenia, immunodeficiency with predominant T cell defect (unspecified), and unspecified immunodeficiency of cell mediated immunity.

[0473] In specific embodiments, DiGeorge anomaly or conditions associated with DiGeorge anomaly are treated, prevented, diagnosed, and/or prognosed using polypeptides or polynucleotides of the invention, or antagonists or agonists thereof.

[0474] Other immunodeficiencies that may be treated, prevented, diagnosed, and/or prognosed using polypeptides or polynucleotides of the invention, and/or agonists or antagonists thereof, include, but are not limited to, chronic granulomatous disease, Chédiak-Higashi syndrome, myeloperoxidase deficiency, leukocyte glucose-6-phosphate dehydrogenase deficiency, X-linked lymphoproliferative syndrome (XLP), leukocyte adhesion deficiency, complement component deficiencies (including C1, C2, C3, C4, C5, C6, C7, C8 and/or C9 deficiencies), reticular dysgenesis, thymic alymphoplasia-aplasia, immunodeficiency with thymoma, severe congenital leukopenia, dysplasia with immunodeficiency, neonatal neutropenia, short limbed dwarfism, and Nezelof syndrome-combined immunodeficiency with Igs.

[0475] In a preferred embodiment, the immunodeficiencies and/or conditions associated with the immunodeficiencies recited above are treated, prevented, diagnosed and/or prognosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention.

[0476] In a preferred embodiment polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention could be used as an agent to boost immunoresponsiveness among immunodeficient individuals. In specific embodiments, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention could be used as an agent to boost immunoresponsiveness among B cell and/or T cell immunodeficient individuals.

[0477] The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, diagnosing and/or prognosing autoimmune disorders. Many autoimmune disorders result from inappropriate recognition of self as foreign material by immune cells. This inappropriate recognition results in an immune response leading to the destruction of the host tissue. Therefore, the administration of polynucleotides and polypeptides of the invention that can inhibit an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing autoimmune disorders.

[0478] Autoimmune diseases or disorders that may be treated, prevented, diagnosed and/or prognosed by polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention include, but are not limited to, one or more of the following: systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, multiple sclerosis, autoimmune thyroiditis, Hashimoto's thyroiditis, autoimmune hemolytic anemia, hemolytic anemia, thrombocytopenia, autoimmune thrombocytopenia purpura, autoimmune neonatal thrombocytopenia, idiopathic thrombocytopenia purpura, purpura (e.g., Henloch-Scoenlein purpura), autoimmunocytopenia, Goodpasture's syndrome, Pemphigus vulgaris, myasthenia gravis, Grave's disease (hyperthyroidism), and insulin-resistant diabetes mellitus.

[0479] Additional disorders that are likely to have an autoimmune component that may be treated, prevented, and/or diagnosed with the compositions of the invention include, but are not limited to, type II collagen-induced arthritis, antiphospholipid syndrome, dermatitis, allergic encephalomyelitis, myocarditis, relapsing polychondritis, rheumatic heart disease, neuritis, uveitis ophthalmia, polyendocrinopathies, Reiter's Disease, Stiff-Man Syndrome, autoimmune pulmonary inflammation, autism, Guillain-Barre Syndrome, insulin dependent diabetes mellitus, and autoimmune inflammatory eye disorders.

[0480] Additional disorders that are likely to have an autoimmune component that may be treated, prevented, diagnosed and/or prognosed with the compositions of the invention include, but are not limited to, scleroderma with anti-collagen antibodies (often characterized, e.g., by nucleolar and other nuclear antibodies), mixed connective tissue disease (often characterized, e.g., by antibodies to extractable nuclear antigens (e.g., ribonucleoprotein)), polymyositis (often characterized, e.g., by nonhistone ANA), pernicious anemia (often characterized, e.g., by antiparietal cell, microsomes, and intrinsic factor antibodies), idiopathic Addison's disease (often characterized, e.g., by humoral and cell-mediated adrenal cytotoxicity, infertility (often characterized, e.g., by antispermatozoal antibodies), glomerulonephritis (often characterized, e.g., by glomerular basement membrane antibodies or immune complexes), bullous pemphigoid (often characterized, e.g., by IgG and complement in basement membrane), Sjogren's syndrome (often characterized, e.g., by multiple tissue antibodies, and/or a specific nonhistone ANA (SS-B)), diabetes mellitus (often characterized, e.g., by cell-mediated and humoral islet

cell antibodies), and adrenergic drug resistance (including adrenergic drug resistance with asthma or cystic fibrosis) (often characterized, e.g., by beta-adrenergic receptor antibodies).

[0481] Additional disorders that may have an autoimmune component that may be treated, prevented, diagnosed and/or prognosed with the compositions of the invention include, but are not limited to, chronic active hepatitis (often characterized, e.g., by smooth muscle antibodies), primary biliary cirrhosis (often characterized, e.g., by mitochondria antibodies), other endocrine gland failure (often characterized, e.g., by specific tissue antibodies in some cases), vitiligo (often characterized, e.g., by melanocyte antibodies), vasculitis (often characterized, e.g., by Ig and complement in vessel walls and/or low serum complement), post-MI (often characterized, e.g., by myocardial antibodies), cardiotomy syndrome (often characterized, e.g., by myocardial antibodies), urticaria (often characterized, e.g., by IgG and IgM antibodies to IgE), atopic dermatitis (often characterized, e.g., by IgG and IgM antibodies to IgE), asthma (often characterized, e.g., by IgG and IgM antibodies to IgE), and many other inflammatory, granulomatous, degenerative, and atrophic disorders.

[0482] In a preferred embodiment, the autoimmune diseases and disorders and/or conditions associated with the diseases and disorders recited above are treated, prevented, diagnosed and/or prognosed using for example, antagonists or agonists, polypeptides or polynucleotides, or antibodies of the present invention. In a specific preferred embodiment, rheumatoid arthritis is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention.

[0483] In another specific preferred embodiment, systemic lupus erythematosus is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention. In another specific preferred embodiment, idiopathic thrombocytopenia purpura is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention.

[0484] In another specific preferred embodiment IgA nephropathy is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention.